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 following four strategies for the prevention of breast cancer (BC) in high-risk women were examined.

Screening: routine screening with mammography for all women.

Tamoxifen: tamoxifen therapy for all women.

Ductal lavage (DL): an attempt of DL for all women, with tamoxifen used only by women with atypia.

Random fine-needle aspiration (rFNA): rFNA for all women, with tamoxifen used only by women with atypia.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of high-risk women (5-year Gail risk \( \geq 1.67\% \)).

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

Dates to which data relate
The effectiveness evidence and some resource use data were derived from studies published between 1990 and 2003. The costs were estimated from sources published between 1995 and 2002. The price year was 2002.

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

Modelling
A Markov model was constructed to simulate the outcomes of survival, quality-adjusted survival and medical costs for a hypothetical cohort of women at high-risk of BC. Three different age groups (40, 50 and 60 years) were modelled. Women could move through various health states. Specifically, healthy/healthy while taking tamoxifen, noninvasive BC, invasive BC, metastatic BC, endometrial cancer, pulmonary embolism, cataracts and death. Women were followed until age 110 or death. The structure of the model was reported. Annual cycles appear to have been used.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the age-specific annual BC rates;
- the stage of invasive disease at diagnosis (node positive or negative);
- the yearly progression rate from noninvasive to invasive BC;
- the yearly progression rate from invasive to metastatic BC (node positive or negative);
- the probability of obtaining atypia on rFNA;
- the probabilities of obtaining nipple aspirate fluid (NAF) if atypia found on rFNA and if no atypia found on rFNA;
- the probability that a NAF-yielding duct is cannulable;
- the probability of finding atypia in a cannulable duct;
- the annual rates of cataract surgery, endometrial cancer (over 50), and pulmonary embolism (over 50) in the general population, and in women taking tamoxifen;
- the yearly mortality rate incurred in addition to age-specific mortality with metastatic BC, endometrial cancer and pulmonary embolism;
- the relative risk for a biomarker for atypia found on rFNA;
- the rate of noninvasive BC (modelled as a fraction of the invasive BC rate); and
- the tamoxifen risk reduction in rates of invasive and noninvasive BC.

Utility weights associated with model health states were also reported.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. The bulk of the evidence came from a clinical trial (the National Surgical Adjuvant Breast and Bowel Project P01 Breast Cancer Prevention Trial). Details of the other studies were not provided. Age-related mortality data came from US Life Tables. The utility weights were obtained from studies that used multiple methods, including time trade-off, standard gamble and rating scales.

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
Nineteen primary studies provided clinical data.
Methods of combining primary studies
It was only stated that a midrange was used when ranges of utility values were found in the literature. Other estimates appear to have been combined using a narrative approach.

Investigation of differences between primary studies
Not stated.

Results of the review
The annual BC rate was 0.00670 in age class 40 - 49, 0.00628 in age class 50 - 50, and 0.00733 in age class 60+ (ranges +/-25%).

At diagnosis, 70% (range: 50 - 90) of patients were node positive and 30% (range: 10 - 50) were node negative.

The yearly progression rate from noninvasive to invasive BC was 0.01 (range: 0.005 - 0.05).

The yearly progression rate from invasive to metastatic BC was 0.04 (range: 0.01 - 0.1) for node positive and 0.1 (range: 0.05 - 0.2) for node negative.

The probability of obtaining atypia on rFNA was 24% (range: 10 - 40).

The probability of obtaining NAF if atypia found on rFNA was 65% (range: 50 - 80).

The probability of obtaining NAF if no atypia found on rFNA was 55% (range: 40 - 70).

The probability that a NAF-yielding duct is cannulable was 92% (range: 75 - 100).

The probability of finding atypia in a cannulable duct was 23% (range: 10 - 40).

In the general population, the annual rate of cataract surgery was 0.0030, endometrial cancer (over 50) 0.00076, and pulmonary embolism (over 50) 0.00031.

In women taking tamoxifen, the annual rate of cataract surgery was 0.00472, endometrial cancer (over 50) 0.00305, and pulmonary embolism (over 50) 0.001.

The yearly mortality rate incurred in addition to age-specific mortality was 0.6 (range: 0.3 - 0.9) with metastatic BC, 0.008 (range: 0.002 - 0.05) with endometrial cancer, and 0.03 (range: 0.001 - 0.05) with pulmonary embolism.

The relative risk for a biomarker for atypia found on rFNA was 3 (range: 2 - 4).

The rate of noninvasive BC (modelled as a fraction of the invasive BC rate) was 40% (range: 25 - 55).

The tamoxifen risk reduction in rates of invasive BC was 49% (range: 35 - 86) in all women and 86% (range: 49 - 86) in women with atypia. The tamoxifen risk reduction of noninvasive BC was 50% (range: 30 - 70) among all women.

The utility weights were as follows:

tamoxifen, 0.97 (range: 0.5 - 1);
noninvasive BC, 0.87 (range: 0.85 - 0.9);
invasive BC, 0.68 (range: 0.65 - 0.95);
metastatic BC, 0.38 (range: 0.3 - 0.6);
endometrial cancer, 0.74 (range: 0.6 - 0.8);
pulmonary embolism, 0.70 (range: 0.3 - 0.9); and
cataracts, 0.80 (range: 0.6 - 0.8).

Methods used to derive estimates of effectiveness
The authors made a key assumption to assess the relative risk of atypia found on lavage.

Estimates of effectiveness and key assumptions
The relative risk of atypia found on lavage was assumed to have been 3 (range: 2 - 4).

Measure of benefits used in the economic analysis
The summary benefit measures used were the life-years (LYs) gained and quality-adjusted life-years (QALYs). Both were derived using a modelling approach. The utility weights were obtained from the literature. An annual discount rate of 3% was applied.

Direct costs
The perspective adopted in the study was not explicitly stated. The economic evaluation considered the costs of diagnostic tests, BC care, cataract surgery, endometrial cancer, pulmonary embolism and tamoxifen. The costs were estimated from published studies, databases and institutions. A detailed breakdown of the cost items was not provided as most of the costs were presented as macro-categories. The unit costs of the tests were reported, but information on resource consumption was unclear. The total costs associated with each prevention strategy were estimated using a modelling approach. All costs were expressed in 2002 values using the Consumer Price Index. Discounting was relevant, owing to the lifetime horizon of the model, and an annual discount rate of 3% was used.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered in the cost analysis.

Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was carried out to examine the robustness of the model to changes in key and uncertain model inputs. Threshold analyses were performed to assess the critical values for those parameters that changed the optimal strategy. Univariate sensitivity analyses were also used to identify the main model drivers. The authors predominantly set the ranges of values used, although some values came from the literature.

Estimated benefits used in the economic analysis
In the cohort starting at age 40, the LYs gained were 39.06 with screening, 39.16 with DL, 39.27 with rFNA and 39.49 with tamoxifen. Incremental life expectancy over screening was 40 days with DL, 79 days with rFNA and 160 days with tamoxifen.
In the cohort starting at age 50, the LYs gained were 30.33 with screening, 30.40 with DL, 30.47 with rFNA and 30.61 with tamoxifen. Incremental life expectancy over screening was 26 days with DL, 51 days with rFNA and 101 days with tamoxifen.

In the cohort starting at age 60, the LYs gained were 21.97 with screening, 22.02 with DL, 22.06 with rFNA and 22.15 with tamoxifen. Incremental life expectancy over screening was 17 days with DL, 33 days with rFNA and 65 days with tamoxifen.

The tamoxifen strategy extended quality-adjusted survival by 129 days for 40-year-olds, 66 days for 50-year-olds and 34 days 60-year-olds, compared with the screening strategy.

The rFNA strategy extended quality-adjusted survival by 76 days for 40-year-olds, 47 days for 50-year-olds and 31 days 60-year-olds, compared with the screening strategy.

The DL strategy extended quality-adjusted survival by 36 days for 40-year-olds, 21 days for 50-year-olds and 13 days 60-year-olds, compared with the screening strategy.

Cost results
The total costs associated with each preventive strategy were not reported.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio (ICER; i.e. the cost per LY gained) was calculated to combine the costs and benefits of the alternative preventive strategies using screening as the reference option. Incremental cost-utility ratios were not calculated.

In the cohort starting at age 40, the ICER over screening was $19,227 with DL, $8,187 with rFNA and $16,531 with tamoxifen.

In the cohort starting at age 50, the ICER over screening was $28,473 with DL, $13,147 with rFNA and $26,813 with tamoxifen.

In the cohort starting at age 60, the ICER over screening was $37,953 with DL, $16,986 with rFNA and $35,275 with tamoxifen.

In all age groups, DL was less effective and more costly than rFNA or tamoxifen, which both had ICERs below the widely accepted threshold of $50,000 per LY gained.

If the proportion of women taking tamoxifen in the tamoxifen strategy was decreased, the cost-effectiveness of such an approach decreased too, while the cost-effectiveness of the risk assessment strategies increased. When the percentages of women willing to take tamoxifen was around 50% and 25% in all age groups, the gains of the tamoxifen strategy were equivalent to those of the rFNA and DL strategies, respectively.

Increasing the relative risk associated with atypia improved the effectiveness of the risk assessment strategies, although it did not change the order.

Less expensive prevention agents and risk assessment costs increased the cost-effectiveness of these strategies.

In general, the rFNA strategy was the most cost-effective, followed by the tamoxifen strategy then the DL strategy. However, if the relative risk that the biomarker conferred was high, then it was more effective to use DL than to offer tamoxifen in women older than 50 years. In older women, the DL strategy was more effective than the tamoxifen strategy when there was a significant differential in the effectiveness of the intervention.

In almost all sensitivity analyses rFNA, DL and tamoxifen showed an ICER lower than $50,000 in comparison with the screening strategy.
Authors' conclusions
If the presence of atypia was truly both a differentiator of breast cancer (BC) risk as well as a predictor of benefit from chemoprevention, then random fine-needle aspiration (rFNA) and ductal lavage (DL) would be particularly useful technologies to improve clinical risk assessment. The tamoxifen strategy led to the highest expected survival, but data suggest that in current practice only a small proportion of women offered tamoxifen choose to take it.

CRD COMMENTARY - Selection of comparators
The choice of the interventions under examination was justified and was consistent with the objective of the study. In particular, FNA was a standard technique used to target areas in the breast for evaluation. The advantages and problems of each diagnostic approach were considered. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data came from a review of the literature. Limited information on the methods and conduct of the review was provided. No details of the search criteria, or the study design and sample in the primary studies were given. Thus, it was not possible to examine the validity of the primary sources. Further, the effectiveness of DL was based on authors' opinions. However, most of the clinical data came from a published clinical trial, which could increase the internal validity of the analysis. The issue of heterogeneity among the primary studies was not addressed. Uncertainty around all clinical inputs was extensively investigated in the sensitivity analysis.

Validity of estimate of measure of benefit
The summary benefit measures used in the economic evaluation were appropriate for assessing the impact of the interventions on patient health. The utility values used to weight survival were obtained from the literature using multiple methods, although details on the sample of individuals from which such values were elicited were not provided. Discounting was applied, as US guidelines recommend.

Validity of estimate of costs
The perspective adopted in the study was not explicitly stated, but only direct medical costs appear to have been included in the economic evaluation. A detailed breakdown of the cost items was not provided as the costs were presented as macro-categories, which is quite common among studies assessing the costs of cancer care. The sources of the cost data were reported. The unit costs of some tests were reported. The costs were treated deterministically and some estimates were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies, although they stated that their results confirmed some research. The issue of the generalisability of the study results to other settings was not addressed. Extensive sensitivity analyses were carried out and the results of the study were clearly reported. This enhances the external validity of the study. However, the total costs were not provided. The study referred to women at high-risk of BC and this was reflected in the authors' conclusions.

Implications of the study
The study results confirmed prior findings that the use of tamoxifen as a chemopreventive agent for BC was cost-effective. However, in clinical settings where women are reluctant to use tamoxifen, risk assessment tools, such as rFNA or DL, would be a cost-effective strategy to prompt a decision to take tamoxifen as a chemopreventive agent. The analysis highlighted that the significance of atypia and other biomarkers and the risk reduction associated with the chemopreventive agent were the main drivers of the model. The authors pointed out that before recommending a risk assessment procedure, it is important to consider whether women would change their decisions about tamoxifen use if...
atypia were found.

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**Bibliographic details**

**Other publications of related interest**


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