Health technology
Tamoxifen therapy for 5 years was compared with usual care without tamoxifen for the prevention of breast cancer among women.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of 10,000 women (with 5,000 using tamoxifen) aged 50 years and older, for whom the 5-year breast cancer risk ranged from 1 to 5%.

Setting
The setting was primary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence data were gathered from studies published between 1983 and 2005. The cost data were taken from published and electronic sources relating to 1999 to 2004, and were adjusted to 2000 prices.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of completed studies.

Modelling
A Markov model was used to estimate the costs and benefits of the intervention and the comparator. The time horizon was the life expectancy at 50 years of age. Each cycle lasted one year. The health states used in the model were reduced risks of invasive breast cancer, ductal carcinoma in situ, and osteoporotic fractures and increased risks of endometrial cancer, deep venous thrombosis (DVT), pulmonary embolism (PE), and cataracts that required surgery.

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

the incidence rates (per 100,000 women per year) of endometrial cancer, PE, DVT, cataracts, osteoporotic fracture, and disability requiring long-term care after hip fracture;
the overall mortality rates (per 100,000 cases per year) of breast cancer (age 50 years and older), endometrial cancer (age 50 years and older), hip fracture (adults) and PE (adults); and

the risk ratio (RR) of breast cancer, DVT, osteoporotic fracture, cataracts, PE and endometrial cancer.

**Study designs and other criteria for inclusion in the review**

A survival analysis (i.e. Surveillance, Epidemiology, and End Results) provided many transition probabilities and mortality rates. Other published studies supplied the remainder. The National Surgical Adjuvant Breast and Bowel Project P-1 trial provided the health outcomes.

**Sources searched to identify primary studies**

Not reported.

**Criteria used to ensure the validity of primary studies**

Not reported.

**Methods used to judge relevance and validity, and for extracting data**

Not reported.

**Number of primary studies included**

Approximately 19 published studies were used to obtain the values for the parameters in the model.

**Methods of combining primary studies**

Not reported.

**Investigation of differences between primary studies**

Not reported.

**Results of the review**

According to the age interval, the incidence rates (per 100,000 women per year) were:

- 75 to 103 for endometrial cancer,
- 20 to 174 for PE,
- 41 to 347 for DVT,
- 182 to 1,220 for cataracts,
- 14.8 to 2,683.9 for osteoporotic fracture, and
- 13,000 for disability requiring long-term care after hip fracture.

According to the years of duration, the overall mortality rates (per 100,000 cases per year; estrogen receptor status adjustment in parentheses) were:

- 2,440 (2,000) to 570 (700) for breast cancer (age >= 50 years), and
3,390 to 890 for endometrial cancer (age >= 50 years).

The overall mortality rates (per 100,000 cases per year) were 20,000 for hip fracture (adults) and 16,000 for PE (adults).

The RR for breast cancer was 0.49 (95% confidence interval, CI: 0.27 to 0.74) for the age range 50 to 59 years, and 0.45 (95% CI: 0.29 to 0.81) for the age range 60 years and older.

The RR for DVT was 1.71 (95% CI: 0.85 to 3.58).

The RR for osteoporotic fracture was 0.79 (95% CI: 0.60 to 1.05).

The RR for cataracts was 1.57 (95% CI: 1.16 to 2.14).

The RR for PE was 3.19 (95% CI: 1.12 to 11.15).

The RR for endometrial cancer was 4.01 (95% CI: 1.70 to 10.90).

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

The summary benefit measure used was the expected number of life-years. These were estimated separately for women with and without a uterus.

**Direct costs**

The direct costs in the economic analysis included the direct medical care costs associated with inpatient, outpatient, and nursing facility care, laboratory procedures, anaesthesiology and other professional services (unspecified), and the drug. The cost data were obtained from published sources. The pricing of tamoxifen was investigated at local pharmacies and at US and Canadian Internet pharmacies. Discounting was carried out at a rate of 3%. The quantities and the costs were not analysed separately. The costs were adjusted to 2000 prices using the medical care component of the Consumer Price Index.

**Statistical analysis of costs**

The costs were treated deterministically. However, the cost of tamoxifen was varied in the sensitivity analysis.

**Indirect Costs**

The indirect costs were not included.

**Currency**

US dollars ($).

**Sensitivity analysis**

Monte Carlo simulations and one-way sensitivity analyses were carried out. One thousand Monte Carlo simulations for 10-year and 50-year intervals, based on theoretical cohorts of 10,000 women with 5,000 using tamoxifen, were used to estimate tamoxifen-related deaths and mortality. The one-way sensitivity analysis investigated the effect on the cost per life-year saved of 5-year breast cancer risk among women age 50 years with and without a uterus. It also investigated the effect on the cost per life-year saved of the price of tamoxifen among women age 50 years with and without a uterus at a 5-year breast cancer risk of 1.67%.

**Estimated benefits used in the economic analysis**

In the base-case, for women with a uterus, the life expectancy was 19.6924 for the strategy without tamoxifen and
In the base-case, for women with a uterus, the life expectancy was 19.7250 for the strategy without tamoxifen and 19.7564 for the strategy with tamoxifen at an AWP of $1,212/year, HMO reimbursement rate of $415/year and Canadian Internet price of US$163/year. The life-years saved were 11.5 days.

Cost results
In the base-case, for women with a uterus, the total costs were:

- $17,695 for the strategy without tamoxifen;
- $23,378 for the strategy with tamoxifen at an AWP of $1,212/year;
- $19,460 for the strategy with tamoxifen at an HMO reimbursement rate of $415/year, and
- $18,221 for the strategy with tamoxifen at a Canadian Internet price of US$163/year.

The incremental costs compared with the no tamoxifen strategy were:

- $5,683 for the strategy with tamoxifen at an AWP of $1,212/year;
- $1,765 for the strategy with tamoxifen at an HMO reimbursement rate of $415/year; and
- $527 for the strategy with tamoxifen at a Canadian Internet price of US$163/year.

In the base-case, for women without a uterus, the total costs were:

- $17,411 for the strategy without tamoxifen;
- $22,963 for the strategy with tamoxifen at an AWP of $1,212/year;
- $19,014 for the strategy with tamoxifen at an HMO reimbursement rate of $415/year; and
- $17,766 for the strategy with tamoxifen at a Canadian Internet price of US$163/year.

The incremental costs compared with the no tamoxifen strategy were:

- $5,552 for the strategy with tamoxifen at an AWP of $1,212/year;
- $1,603 for the strategy with tamoxifen at an HMO reimbursement rate of $415/year; and
- $355 for the strategy with tamoxifen at a Canadian Internet price of US$163/year.

Synthesis of costs and benefits
The incremental cost per life-year saved was calculated in order to combine the costs and benefits.

In the base-case, for women with a uterus, the incremental cost per life-year saved over the strategy without tamoxifen was:

- $1,335,690 for the strategy with tamoxifen at an AWP of $1,212/year;
- $414,916 for the strategy with tamoxifen at an HMO reimbursement rate of $415/year; and
$123,780 for the strategy with tamoxifen at a Canadian Internet price of US$163/year.

In the base-case, for women without a uterus, the incremental cost per life-year saved over the strategy without tamoxifen was:

$177,116 for the strategy with tamoxifen at an AWP of $1,212/year;

$51,146 for the strategy with tamoxifen at an HMO reimbursement rate of $415/year; and

$11,315 for the strategy with tamoxifen at a Canadian Internet price of US$163/year.

The sensitivity analysis in which the 5-year breast cancer risk score was varied indicated that tamoxifen was dominated for women with a uterus until the 5-year breast cancer risk reached 2.1% or more. In addition, when the projected benefits of tamoxifen were limited to 5 years' duration, tamoxifen was dominated until the 5-year breast cancer risk reached 3%.

The sensitivity analysis around the tamoxifen price showed that the tamoxifen price needed to be $144/year to achieve an incremental cost-effectiveness ratio of $100,000 per life-year saved for women with a uterus and a 5-year breast cancer risk of 1.67%.

Authors' conclusions
Tamoxifen may increase mortality in women at the lower end of the "high-risk" range for breast cancer. The use of tamoxifen in women with a 5-year risk greater than 3% could be a reasonable strategy to reduce the incidence of breast cancer if the tamoxifen price is low enough.

CRD COMMENTARY - Selection of comparators
The rationale for choosing no tamoxifen as the comparator was clear as 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
It was unclear if a systematic review of the literature was undertaken. Although this is common practice with modelling studies, it does not always ensure that the best data available are used in the model. However, all sources used to derive the estimates were clearly stated, with ranges being given as appropriate. Extensive sensitivity analyses were undertaken and this increases the validity of the results.

Validity of estimate of measure of benefit
The use of life-years as the summary benefit measure appears to have been appropriate as life expectancy is a widely used benefit measure. The life expectancy was determined from the model using appropriate input parameters. However, the use of quality-adjusted life-years to measure the benefit would have facilitated comparisons with other health care interventions.

Validity of estimate of costs
The authors stated that a payer's perspective was adopted in the study. All the relevant categories of costs seem to have been included in the analysis. The quantities and the costs were not analysed separately, which may limit the generalisability and transferability to other settings. The sensitivity analysis on the variation of drug price was appropriately conducted. Discounting was relevant and was undertaken. The price year was also given, which should strengthen the reproducibility of the study results.

Other issues
The authors compared their findings with those from other studies and stated that similar conclusions had been drawn.
They acknowledged some limitations of their study. For example, the lack of consideration of the effects of tamoxifen on quality of life and the costs of time lost from work, and the potential for an increased risk of stroke from the use of tamoxifen. The results were particularly sensitive to the price of tamoxifen.

**Implications of the study**

The authors suggest that, as a chemoprevention agent, tamoxifen is cost-effective only for those with a sufficiently high risk of breast cancer. More research is needed to assess the quality of life and the effects of lost productivity for this drug/patient domain.

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**Other publications of related interest**

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