The cost effectiveness of tamoxifen in the prevention of breast cancer
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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
The use of tamoxifen, 10 mg twice daily, was compared with placebo for the prevention of breast cancer.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis

Study population
The patient population comprised women considered to be at increased risk of developing breast cancer. These include all women aged 60 years or older, or those aged 35 to 59 years with a history of lobular carcinoma in situ or other factors that made their predicted 5-year breast cancer rate the same as that of a 60-year old woman (1.66%).

Setting
The setting was not explicitly stated but, presumably, prophylactic tamoxifen could be prescribed in primary care. The economic study was carried out in Chicago, Illinois, USA.

Dates to which data relate
The effectiveness data were derived from the results of a trial conducted between 1992 and 1998 (see Other Publications of Related Interest). The mortality data were derived from studies and other sources published between 1995 and 1998. The cost data were derived from studies and other sources published between 1993 and 1998. The prices were in 1997 US dollars ($).

Source of effectiveness data
The effectiveness data were derived from the published results of a single trial, published mortality data, and assumptions.

Link between effectiveness and cost data
The costing data were derived from published studies that did not use the same patient sample as that used in the effectiveness study. The exception was the resource use data for tamoxifen therapy, which related to the trial protocol.

Modelling
A multistage Markov model was developed to estimate the annual progression to various disease states and death, and the associated costs.
Outcomes assessed in the review
The outcomes assessed in the review were the incidence rates of:

- invasive and non-invasive breast cancer,
- endometrial cancer,
- pulmonary embolism,
- cataract surgery,
- fractures (hip, Colles or spinal),
- stroke,
- deep vein thrombosis,
- overall mortality, and
- mortality from medical events (except cataract surgery and Colles fracture).

Study designs and other criteria for inclusion in the review
The study designs included in the review were a multi-centre randomised controlled trial (RCT) of tamoxifen and placebo, clinical trials of patients with other medical events, and national data sets.

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
Twelve studies were included in the review.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
The authors did not investigate the differences between the primary studies.

Results of the review
The incidence rates for all women were:

for invasive breast cancer, 0.343% (tamoxifen) and 0.676% (placebo);
for non-invasive breast cancer, 0.135% (tamoxifen) and 0.268% (placebo);
for endometrial cancer, 0.230% (tamoxifen) and 0.091% (placebo);
for pulmonary embolism, 0.069% (tamoxifen) and 0.023% (placebo);
for hip fracture, 0.046% (tamoxifen) and 0.084% (placebo);
for Colles fracture, 0.054% (tamoxifen) and 0.088% (placebo);
for spinal fracture, 0.088% (tamoxifen) and 0.118% (placebo);
for deep vein thrombosis, 0.134% (tamoxifen) and 0.084% (placebo); and
for stroke, 0.145% (tamoxifen) and 0.092% (placebo).

The annual mortality rates for the first five years from the time of the medical event diagnosis were 5.0% (invasive breast cancer), 0.6% (non-invasive breast cancer), and 2.8% (endometrial cancer).

The overall mortality rates for the first five years from the time of the medical event diagnosis were:
for hip fracture, 0% (age: 35 - 49 years), 4.5% (age: 50 - 59 years), and 9.0% (age: 60 - 69 years);
for spinal fracture, 3.1%; and
for stroke, 10.0%.

The mortality rates for the first year from the time of the medical event diagnosis (thereafter 0%) were 2.3% (pulmonary embolism) and 0.5% (deep vein thrombosis).

**Methods used to derive estimates of effectiveness**
The effectiveness estimates were derived from authors' assumptions.

**Estimates of effectiveness and key assumptions**
The authors assumed that the effects of tamoxifen lasted 5 years (i.e. only while the women were taking the drug), after which time their incidence rates matched those of the women on placebo. This was varied to 10 years in the sensitivity analysis. The authors also assumed that patients did not die from cataract surgery or Colles fracture.

**Measure of benefits used in the economic analysis**
The health benefit measure used was the life-years gained.

**Direct costs**
The analysis included the direct medical costs of tamoxifen and treating medical events, to all payers. Apart from tamoxifen, the resource quantities were not reported. The costs of tamoxifen and breast cancer treatment were related to the duration of survival, whereas the duration of the other costs was not reported. The cost of treating each medical event was derived from a single article. The tamoxifen costs were derived from a weighted average of wholesale prices for brand and generic products. All sources were published between 1993 and 1998. The costs were adjusted for inflation using the Medical Care Services Consumer Price Index and were reported in 1997 US dollars. In the base-case, both the costs and the benefits were discounted at an annual rate of 3%.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way simple sensitivity analyses were carried out on several model parameters. In the multi-centre RCT, there were no significant differences in the incidence rates of fractures (hip, wrist and spine), deep vein thrombosis, and stroke. The costs of these events were only included in the sensitivity analysis.

The assumed duration of the effects of tamoxifen (5 years) was increased to 10 years.

All death rates were increased and decreased simultaneously by 20% to account for variability in the data. The mortality rates for breast cancer were decreased by 25% independently.

Due to differences in the general opinion over the rates that should be used, three alternative discount rate scenarios were analysed. The three scenarios were no discounting, discounting the costs only by 3%, and discounting both the costs and the benefits by 5%.

All the costs were increased and decreased by 20% to account for variability in cost estimates.

The effectiveness of tamoxifen was increased and decreased by 10% to analyse the effect on populations with different risk profiles.

**Estimated benefits used in the economic analysis**
With tamoxifen, the women gained 0.0670 life-years (5-year tamoxifen effect) and 0.1136 life-years (10-year tamoxifen effect) when compared with placebo. The gains were:

- 0.1028 years (5-year effect) and 0.1800 years (10-year effect) in women aged 35 to 49;
- 0.0624 years (5-year effect) and 0.1048 years (10-year effect) in women aged 50 to 59; and
- 0.0538 years (5-year effect) and 0.0845 years (10-year effect) in women aged 60 to 69.

In women who had undergone a hysterectomy, the gains assuming a 5-year effect were 0.1060 years (all women), 0.0846 years (age: 35 - 49), 0.0697 years (age: 50 - 59) and 0.0906 years (age: 60 - 69). The gains assuming a 10-year effect were 0.0906 years (all women), 0.1857 years (age: 35 - 49), 0.1429 years (age: 50 - 59) and 0.1102 years (age: 60 - 69).

The results were extrapolated beyond the trial data to a maximum of 90 years of age using age- and disease-specific mortality rates. The side-effects of treatment were considered as adverse medical events that, via mortality, affected the life-year estimates.

**Cost results**
The estimated lifetime discounted cost per patient with tamoxifen therapy (5-year effect) was $10,509, compared with $6,228 without tamoxifen, producing an incremental cost of $4,281. The other base-case incremental costs included $4,253 for women aged 35 to 49, $4,265 for women aged 50 to 59, and $4,034 for women aged 60 to 69.

**Synthesis of costs and benefits**
The incremental costs per life-year gained were estimated for age- and hysterectomy-status subgroups. Under the base-case assumptions, tamoxifen had an incremental cost per life-year gained of $41,372 for women aged 35 to 49, $68,349
for women aged 50 to 59, and $74,981 for women aged 60 to 69. Tamoxifen was more cost-effective in women aged 35 to 49 and women who had undergone a hysterectomy. The base-case incremental cost per life-year gained (all women: $63,896) was most sensitive to the choice of discount rates (range: $37,851 - $87,095), the decrease in breast cancer mortality rates ($88,374), and variations in the medical costs (range: $37,977 - $90,301).

Authors' conclusions
The use of preventive tamoxifen in high-risk women, particularly those aged 35 to 49 and those who have had a hysterectomy, falls within acceptable cost-effectiveness boundaries. Preventive tamoxifen should be offered when deemed beneficial by the doctor and patient.

CRD COMMENTARY - Selection of comparators
Placebo was a valid comparator as, in many settings, there are no commonly used pharmacological options for the prevention of breast cancer.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. This article omitted several details about the design of the RCT. These included the use of power calculations, the methods of randomisation, and the comparability of the intervention and control groups. The authors justified their assumptions with reference to the medical literature. The estimates were investigated by sensitivity analyses, the ranges for which appear to have been appropriate.

Validity of estimate of measure of benefit
The estimation of benefits was modelled and the modelling was largely appropriate. However, a limitation of the model was that it used trial data to populate a lifetime model. There is uncertainty about the duration of the effect of tamoxifen, as highlighted by the authors' use of a wide range for this variable in the sensitivity analysis.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted appear to have been included in the analysis. The resource use quantities were not reported, which limited the generalisability of these costs to other settings. The authors did not report their rationales for selecting the single articles used to derive each treatment cost, but they did subject these costs to a sensitivity analysis. The price year was reported.

Other issues
The model was well explained and could be used as a basis for models in other countries or patient populations. The authors cited only a small number of cost-effectiveness studies on preventive interventions. They did, however, make some comparisons between their cost-effectiveness ratios and those in other disease areas. The issue of generalisability to other settings was not addressed. The authors did not present their results selectively. The tamoxifen trial enrolled women at high risk of breast cancer and this was reflected in the authors' conclusions. The sensitivity analyses were extensive and were described in detail. However, these analyses were one-way and yielded a wide range of incremental cost-effectiveness ratios. This made the analysis difficult to interpret. It would have been helpful if the authors had attached likelihoods to the parameter estimates. The authors acknowledge that the cost-effectiveness of tamoxifen may be greater if quality of life and indirect costs had been considered.

Implications of the study
The authors conclude that tamoxifen should be available for the prevention of breast cancer in high-risk women. They also speculate on the cost-effectiveness of this therapy in women whose risk is higher than that required to participate in the multi-centre RCT, and suggest further research on this topic.
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Other publications of related interest

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