Tamoxifen for breast cancer prevention: a framework for clinical decisions

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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 (20 mg/day), taken for 5 years, as chemoprevention for women at risk of breast cancer.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The model analysed data for a hypothetical cohort of women aged 50 years, with an estimated 5-year breast cancer risk of 3.4%, who had an intact uterus. This represented the average patient in the Breast Cancer Prevention Trial.

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 1979 and 2001. The cost data were taken from published and electronic sources relating to 1996 to 2002, and were adjusted to 2002 prices.

Source of effectiveness data
The estimates for the final outcomes were derived from a synthesis of published studies.

Modelling
A Markov model was used to estimate the costs and benefits for the intervention and the comparator. The time horizon was the average remaining life expectancy. Each cycle lasted one year. Nine health states were used in the model:

- well on tamoxifen therapy;
- well off tamoxifen;
- breast cancer with varying tumour size;
- deep vein thrombosis (DVT) with or without post-phlebitic syndrome;
- pulmonary embolism (PE);
- endometrial cancer;
stroke with mild; moderate or severe debility;

breast cancer cured; and

death.

The model assumed that tamoxifen was stopped for patients who experienced complications with the drug, and started for those who developed breast cancer. The patients were then exposed to the probabilities associated with their new regimen.

**Outcomes assessed in the review**
The outcomes assessed from an ad hoc review of the literature were:

- the probabilities of breast cancer, endometrial cancer, PE, DVT and stroke, with and without tamoxifen therapy;
- the probabilities that a breast cancer tumour was of size 0 - 1.0 cm, 1.1 - 2.0 cm, 2.1 - 3.0cm, or greater than 3.0 cm, with and without tamoxifen therapy;
- the probabilities that with breast cancer cure, the tumour size was 0 - 1.0 cm, 1.1 - 2.0 cm, or greater than 2.1 cm; and
- the probabilities of endometrial cancer cure, post-phlebitic syndrome, and death from PE.

**Study designs and other criteria for inclusion in the review**
The Breast Cancer Prevention Trial of the National Adjuvant Breast and Bowel Project provided most of the annual transition probabilities. Other published studies supplied the rest.

**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**
The values for the parameters in the model were obtained from 10 published studies.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The following probabilities were used in the model:
with tamoxifen therapy, the probability of breast cancer was 0.0034 (range: 0.002 - 0.006), endometrial cancer 0.0031 (range: 0.0015 - 0.0031), PE 0.0010 (range: 0.0004 - 0.0012), DVT 0.0015 (range: 0.001 - 0.0018) and stroke 0.0022 (range: 0.0013 - 0.0022);

without tamoxifen therapy, the probability of breast cancer was 0.0068 (range: 0.004 - 0.012), endometrial cancer 0.00076, PE 0.0003, DVT 0.0009 and stroke 0.0013 (range: 0.0008 - 0.0013);

with tamoxifen therapy, the probability was 0.42 that a breast cancer tumour was of size 0 - 1.0 cm, 0.30 for size 1.1 - 2.0 cm, 0.16 for size 2.1 - 3.0 cm and 0.12 for size greater than 3.0 cm;

without tamoxifen therapy, the probability was 0.36 that a breast cancer tumour was of size 0 - 1.0 cm, 0.39 for size 1.1 - 2.0 cm, 0.14 for size 2.1 - 3.0 cm and 0.11 for size greater than 3.0 cm;

with breast cancer cure, the probability was 0.95 (range: 0.50 - 0.97) that the tumour size was 0.0 - 1.0 cm, 0.79 for size 1.1 - 2.0 cm and 0.68 for size greater than 2.1 cm;

the probability of endometrial cancer cure was 0.80 (range: 0.60 - 0.95);

the probability of post-phlebitic syndrome was 0.70 (range: 0.30 - 0.90); and

the probability of death from PE was 0.20 (range: 0.05 - 0.40).

Measure of benefits used in the economic analysis
The measure of health benefit used was the quality-adjusted life-years (QALYs) gained. These were obtained from the model.

The authors undertook a survey to determine utility valuations for most of the health outcomes in the model. They interviewed 106 women from the general public in North Carolina and south Florida using the standard gamble methodology. The women were aged at least 50 years, represented a range of income and educational levels, and comprised at least 33% African-Americans. The authors reported the health utility scores obtained. In addition, utility scores for post-phlebitic syndrome and hip fractures were obtained from prior publications. The benefits were not discounted.

Direct costs
The direct costs of health care were evaluated. The costs included in the analysis were the annual cost of tamoxifen and the lifetime costs of treating breast cancer, stroke, DVT, PE and endometrial cancer. The drug costs were taken from average wholesale prices and increased by 8% to simulate retail pricing. All other costs came from four published studies. The cost estimates were reported separately from other model parameters. Discounting was not applied, even though the costs were incurred during more than two years. The costs were adjusted to 2002 prices, but the method used was not reported.

Statistical analysis of costs
No statistical analysis of the costs was conducted to compare the costs in the two groups.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).
Sensitivity analysis
A sensitivity analysis was conducted to investigate variability in the data, and to extrapolate from the primary trial to make the results more comprehensive. The methods used were not described. The age of the patient, transition probabilities, key model assumptions, health utility scores and the estimates of costs were investigated in the sensitivity analysis. The authors did not justify the ranges over which the variables were tested. However, they were not based on a synthesis of the literature, as in most instances the parameter estimate was derived from a single study.

Estimated benefits used in the economic analysis
The undiscounted QALYs gained were 26.07 with tamoxifen chemoprevention and 25.97 without tamoxifen chemoprevention. The authors calculated the duration of benefits over the patient's lifetime.

Cost results
The authors did not report the total cost of the intervention or the comparator.

Synthesis of costs and benefits
The authors reported that the cost-effectiveness ratio was $43,300 per QALY. They did not describe how they obtained this value. Discounting was not applied.

The sensitivity analysis showed that prophylactic tamoxifen therapy was not cost-effective for older women (50 - 65 years), owing to the high risk of endometrial cancer, and when the cure rate for endometrial cancer dropped to 60%. The intervention became more cost-effective as the lifetime costs of breast cancer increased, when utility scores for curable breast cancer decreased, and when the risk of breast cancer was high.

Authors' conclusions
Given a cost-effectiveness threshold of $50,000, tamoxifen chemoprevention is cost-effective for women aged 40 - 50 years who have 5-year risk of breast cancer of at least 3.4%. The cost-effectiveness for older women depends on the patient's risk of breast cancer, fear of breast cancer, and the presence of the uterus. Tamoxifen chemoprevention is contraindicated for patients with a high risk of stroke or a hyper-coagulable state.

CRD COMMENTARY - Selection of comparators
The authors chose "no treatment" as the comparator for tamoxifen chemoprevention in order to replicate the clinical trial on which this study was based. This comparator could be justified if tamoxifen chemoprevention represented a new adjunctive therapy rather than a substitute for an existing therapy. The authors could have chosen another prophylactic therapy for breast cancer as the comparator, such as bilateral mastectomy. You should decide if "no treatment" represents current practice in your own setting.

Validity of estimate of measure of effectiveness
A systematic review of the literature was not undertaken. Although this is a common practice with models, it does not always ensure that the best data available are used in the model. The authors frequently derived their estimates from a single study, without discussing the quality of its methodology. Therefore, it was not possible to evaluate the validity of the input parameters for the effectiveness model. A sensitivity analysis was conducted on many of the parameters, but it was unclear how the ranges were derived and whether they were appropriate.

Validity of estimate of measure of benefit
The summary measure of benefit was the QALYs, which were derived directly from the model. The utility values for the different health outcomes were established in a survey by the authors using the standard gamble technique.
Validity of estimate of costs
The study perspective was not stated. Consequently, it was not possible to determine whether all the relevant categories of costs were included in the analysis. The cost estimates were reported separately from other model parameters. The total lifetime costs associated with the health states were reported in an aggregated manner, which may limit the reproducibility of the study results. These costs were obtained from different studies and it was unclear whether the studies were comparable in terms of which costs had been included, especially as they were undertaken in different countries. No statistical tests were conducted on the costs. A sensitivity analysis was conducted to assess the robustness of the results when the estimated costs were modified. The ranges used were not justified and it was not possible to determine whether they were appropriate.

Discounting was not applied, which was inappropriate given the long follow-up. It was not possible to determine whether costs or charges were reported. The costs were adjusted to a single price year, but the methodology used to achieve this was not reported. Of concern was the authors' failure to report the total cost of the intervention and the comparator, as calculated from the model. This decreases the transparency of the study and limits the transferability of the study results to other settings. The study would have been improved had the principals of economic analysis been applied, as a major weakness of the study was the cost analysis.

Other issues
The authors did not compare their findings with those from other studies, so it is not known how far their results agreed with those of published studies. They also did not directly address the issue of the generalisability of the results to other settings. The authors failed to report the total costs of the intervention and the comparator. The authors acknowledged that the clinical trial on which their study was based had reported different results to other trials. For example, other trials had not found the same breast cancer risk reduction with tamoxifen chemoprevention, and one also reported excess mortality in the intervention group. However, the authors discussed the reasons why they found the Breast Cancer Prevention Trial (Fisher et al. 1998) to be the most reliable source of efficacy data.

Implications of the study
The authors suggested that tamoxifen chemoprevention is likely to be underused in patients under 50 years of age. They proposed five age-related guidelines for its clinical use and suggested that future research should focus on agents such as selective oestrogen receptor modulators and aromatase inhibitors, which are more appropriate for patients over 60 years.

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