Decision analysis of tamoxifen for the prevention of invasive breast cancer

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 orally, twice daily) to reduce recurrence rates and prolong survival in breast cancer patients, with relatively mild side effects. Tamoxifen is an oestrogen-receptor modulator that is approved by the Food and Drug Administration.

Type of intervention
Primary prevention.

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

Study population
The study population comprised women aged older than 35 years and at high risk for breast cancer. High risk was defined using the model of Gail et al. (see Other Publications of Related Interest no.2), which predicts risk on such factors as age, the number of first-degree relatives with breast cancer, nulliparity or age at first live birth, and the number of breast biopsies.

Setting
The setting was the community. The economic study was carried out at Columbia University, New York, USA.

Dates to which data relate
The effectiveness and resource use data were gathered from studies published in 1997 and 1998. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from published studies and some experts' opinions.

Modelling
A Markov model and 500 Monte Carlo simulations were used to simulate the natural history of three cohorts of patients who were administered tamoxifen or placebo to prevent breast cancer in the first year of each age range. The age ranges were 35 to 49 years, 50 to 59 years, and 60 years or older. The long-term effects on the (quality-adjusted) survival and the expected costs were estimated. Nine health states were considered in the model. These included good health, good health after stopping tamoxifen, non-invasive breast cancer, invasive breast cancer, hip fracture, thrombophlebitis or pulmonary emboli, endometrial cancer, cataracts, and death. The time horizon of the model was 100 years or death. A group of clinical oncologists supported the development of the model. The side effects or potential benefits of tamoxifen that did not reach statistical significance in the BCPT, such as osteoporosis, cardiovascular disease and stroke, were excluded from the model.
Outcomes assessed in the review
The outcomes assessed in the review were also used as inputs to the model. The outcomes assessed were:

- the transition rate among health states (from well to breast cancer) in each age class;
- the survival projections for those women who developed breast or endometrial cancer;
- the percentage of women initially diagnosed with breast cancer that were node-negative;
- the effect of oestrogen receptor status on survival; and
- the quality of life estimates associated with different health states, as derived using a time-trade-off questionnaire.

Study designs and other criteria for inclusion in the review
Not reported.

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 effectiveness evidence were derived mainly from twelve primary studies.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
In the groups treated with tamoxifen, the transition rate from well to breast cancer was 0.00377 in the age class 35 to 49 years, 0.00310 in the age class 50 to 59 years, and 0.00333 in the age class 60 years and over.

In the groups administered placebo, the transition rate from well to breast cancer was 0.00670 in the age class 35 to 49 years, 0.00628 in the age class 50 to 59 years, and 0.00733 in the age class 60 years and over.

The survival projections for those women who developed breast or endometrial cancer were not reported separately.

The percentage of women initially diagnosed with breast cancer who were node-negative was 70% (30% were node-positive).

The effect of oestrogen receptor status on survival was considered "minimal".
Finally, the preference rating (assigned by healthy women) was 1 for perfect health, 0.79 for chemoprevention, 0.68 for breast cancer, 0.52 for metabolic breast cancer, and 0 for death.

The ratings for the other health states used in the model were 0.68 for endometrial cancer, 0.50 for pulmonary emboli, 0.68 for cataract surgery, and 0.28 for hip fracture from osteoporosis.

**Methods used to derive estimates of effectiveness**
The authors made several assumptions in the construction of the decision model, which were supported by a panel of clinical oncologists.

**Estimates of effectiveness and key assumptions**
The panel of clinical oncologists was used to support the estimations relating to the transition probabilities among the health states. The other assumptions made were as follows:

- the beneficial effects of taking tamoxifen for 5 years would last for only 5 years;
- patients who developed endometrial cancer, thrombophlebitis or pulmonary emboli, or cataracts would discontinue tamoxifen use immediately;
- these side effects would only occur during treatment;
- women who discontinued tamoxifen would not experience any of its health benefits;
- women who developed these complications had the same risk of breast cancer as other women; and
- the women who developed breast cancer would have the mortality risk associated with breast cancer.

**Measure of benefits used in the economic analysis**
The benefit measures used in the economic analysis were the incremental survival and the incremental quality-adjusted survival. These were both discounted at 3% to calculate the present value of future life-years. The values used to calculate the utility scores for the quality adjustment were mainly those of healthy women, derived using a time-trade-off questionnaire.

**Direct costs**
The future costs were discounted at a rate of 3%. The unit costs and the resources were not reported separately. The cost/resource boundary adopted was unclear. The cost analysis included the cancer costs, non-cancer costs (yearly and terminal costs), and other medical costs related to the costs of treating complications. The cancer costs covered the first year of care after diagnosis, yearly continuing care costs, and terminal care costs in the last year of life. The costs were estimated using actual data derived from official publications of the Health Care Financing Administration. The quantities were estimated from data published in 1997 and 1998. The total costs of each procedure were derived using modelling. All the costs were adjusted to the Medical Consumer Price Index for 1998, which was also the price year.

**Statistical analysis of costs**
No statistical analysis of the costs was reported.

**Indirect Costs**
No indirect costs were included.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way sensitivity analyses were carried out to assess the effect of various model parameter values on the incremental cost-effectiveness ratios. The parameters varied were the duration of the effects of tamoxifen (10, 15 years), the preferences for health states (0.81, 0.83, 0.59), and the cost of tamoxifen (+20%, -20%, -40%).

**Estimated benefits used in the economic analysis**
The incremental mean survival of tamoxifen over placebo was 69 days (median 69; 95% confidence interval, CI: 27 - 117) starting at age 35, 40 days (median 41; 95% CI: 16 - 67) starting at age 50, and 27 days (median 27; 95% CI: 14 - 40) starting at age 60.

The incremental mean quality-adjusted survival of tamoxifen over placebo was 38 days (median 38; 95% CI: 0.2 - 82) starting at age 35, 25 days (median 25; 95% CI: 0 - 50) starting at age 50, and 22 days (median 22; 95% CI: 5 - 39) starting at age 60.

**Cost results**
The total expected costs of tamoxifen or placebo were not reported.

The cancer costs were as follows.

In the age class 35 to 49 years: the first year of care cost $17,762, yearly continuing care cost $5,492, and the terminal care in the last year of life cost $38,654.

In the age class 50 to 64 years: the first year of care cost $16,736, yearly continuing care cost $5,048, and the terminal care in the last year of life cost $29,811.

In the age class 65 to 79 years: the first year of care cost $15,616, yearly continuing care cost $5,624, and the terminal care in the last year of life cost $23,936.

In the age class 80 years and over: the first year of care cost $15,080, yearly continuing care cost $6,892, and the terminal care in the last year of life cost $16,101.

The non-cancer costs were as follows:

in the age class 35 to 49 years, the yearly costs were $1,881 and the terminal care costs were $35,413;

in the age class 50 to 64 years, the yearly costs were $2,821 and the terminal care costs were $27,311; and

in the age class 65 to 79 years, the yearly costs were $5,094 and the terminal care costs were $21,929 (subclass 65 to 74 years) and $19,045 (subclass 75 to 79 years); and

in the age class 80 years and over, the yearly costs were $6,662 and the terminal care costs were $13,748.

Finally, the other medical costs were $5,013 for endometrial cancer, $4,175 for pulmonary emboli, $3,095 for cataract surgery, $10,376 for hip fracture surgery, and $10,844 for non-invasive breast cancer.

**Synthesis of costs and benefits**
The costs and the benefits were combined using incremental cost-effectiveness and cost-utility analyses.

The incremental mean cost per life-year of tamoxifen over placebo was $46,619 (median $49,206; 95% CI: 27,928 - 98,796) starting at age 35, $82,748 (median $86,183; 95% CI: 50,215 - 218,102) starting at age 50, and $122,401
The incremental mean cost per quality-adjusted life-year of tamoxifen over placebo was $76,318 (median $80,939; 95% CI: 37,810 - 4,178,041) starting at age 35, $130,660 (median $130,076; 95% CI: 61,247 - 11,875,082) starting at age 50, and $142,227 (median $143,293; 95% CI: 72,884 - 1,316,519) starting at age 60.

Assuming 10 years of benefits with tamoxifen, the average cost per life-year was $25,727 starting at the age of 35, $49,460 starting at the age of 50, and $94,320 starting at the age of 60.

Assuming 10 years of benefits with tamoxifen, the average cost per quality-adjusted life-year was $33,025 starting at the age of 35, $57,356 starting at the age of 50, and $82,504 starting at the age of 60.

Assuming 15 years of benefits with tamoxifen, the average cost per life-year was $16,160 starting at the age of 35, $38,898 starting at the age of 50, and $90,600 starting at the age of 60.

Assuming 15 years of benefits with tamoxifen, the average cost per quality-adjusted life-year was $18,788 starting at the age of 35, $41,115 starting at the age of 50, and $67,036 starting at the age of 60.

Variations in the cost of tamoxifen and preferences for tamoxifen also affected the study's results. Raising the cost by 20% produced a minimum value of $102,971 per QALY for age 35, and a maximum value of $175,338 for age 60. Reducing the cost by 40% produced a minimum value of $38,517 per QALY for age 35, and a maximum value of $82,323 for age 60. Using the set of preferences given produced a minimum value of $76,292 for age 35, and a maximum value of $869,674 for age 60.

Authors’ conclusions
Tamoxifen was effective in improving the survival in patients of all age classes. However, it appeared to be cost-effective only in those women who started the treatment at a relatively early age (35 years), in comparison with other accepted cancer preventive practices.

CRD COMMENTARY - Selection of comparators
The reason for the selection of the comparator was clear. A placebo was selected, as in the BCPT study (see Other Publications of Related Interest no.1). You should assess whether it represents a widely used technology in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from several published studies, but a review of the literature was not conducted. Some estimations were combined, although the method used to perform the synthesis was not reported. Some problems could arise from the fact that some preferences for health states were derived from healthy women, and then applied to a specific population of patients at high risk for breast cancer. Also, expert opinion was used, which might be questionable given the incomplete evidence of a systematic literature search.

Validity of estimate of measure of benefit
The economic benefit of the study was represented by the number of life-years gained with the use of tamoxifen, adjusted by preferences. These benefit measures appear to have been appropriate for the study question. The Markov model, which was used to simulate the natural history of the disease progression, also appears to have been useful. The sensitivity analysis revealed a large range in the incremental cost-effectiveness ratios, which depended on preference weights.

Validity of estimate of costs
The estimation of the costs was quite specific to the study setting. Sensitivity analyses were only conducted on the price of tamoxifen. In addition, since the perspective of the study was unclear, some of the cost components could have been...
omitted or erroneously included in the analysis. Statistical analyses on the prices and the quantities were not conducted. In addition, for numerous categories of costs, the (DRG) reimbursement rates were used, rather than the unit costs per resource quantity.

Other issues
The authors compared their findings with those from other studies. The issue of the generalisability of the study results to other settings was not explicitly addressed and, despite sensitivity analyses being conducted on some model inputs, the external validity of the study might be impaired. The study would have benefited from presenting the resource quantities and the unit costs, although most of the effectiveness results were given.

Implications of the study
According to the authors, chemoprevention using tamoxifen should be limited to young patients at high risk for breast cancer. "The benefits of tamoxifen chemoprevention for women older than 60 years are minimal and expensive from a health policy perspective". In addition, the authors showed that, like other oestrogen-receptor modulators, tamoxifen would reduce the risk of osteoporosis and fractures in postmenopausal women. These remarks should be viewed in the light of the caveats highlighted.

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Other publications of related interest


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