Outcomes of tamoxifen chemoprevention for breast cancer in very high-risk women: a cost-effectiveness analysis

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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, a chemopreventive agent used to decrease the risk of invasive breast cancer.

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 women at high-risk of developing breast cancer. Four subgroups of women were considered:

- women with atypical ductal hyperplasia (group 1),
- women with lobular carcinoma-in-situ (group 2),
- women assessed as having Gail risk greater than 5 (group 3), and
- women with two or more first-degree relatives with breast cancer (group 4).

Setting
The setting, although not explicitly reported, is likely to have been primary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness evidence was derived from studies published between 1992 and 1999. Dates relating to resource consumption were not reported. The price year was 1998.

Source of effectiveness data
The effectiveness evidence came from published studies and the authors' assumptions.

Modelling
A decision model based on Markov cycles was constructed to predict the costs, survival and quality-adjusted survival of a hypothetical cohort of 1,000 women at high-risk of developing breast cancer. Patients used tamoxifen as primary prevention and were compared with women receiving no intervention. The model simulated economic and clinical
outcomes up to a patient age of 100 years or death. The health state outcomes were good health, good health after stopping tamoxifen, non-invasive and invasive breast cancer, hip fracture, thrombophlebitis/pulmonary emboli, endometrial cancer, cataracts, and death. The model considered three age ranges for starting tamoxifen. These were 35 to 49 years, 50 to 59 years, and 60 years or over.

**Outcomes assessed in the review**
The outcomes estimated from published studies and used as model inputs were as follows:

- the incidence rates of invasive breast cancer in the three age groups and in the four high-risk groups;
- the incidence of non-invasive breast cancer, endometrial cancer, pulmonary embolism, cataracts and hip fracture;
- mortality rates due to breast cancer, endometrial cancer, non-invasive breast cancer, pulmonary emboli, cataracts and hip fracture;
- the probability of other conditions (such as breast cancer stage at diagnosis, effect of ER status on survival, more than one outcome); and
- the duration of tamoxifen benefit.

The preference ratings used for the health states considered in the decision model were also derived from published studies. The health states were perfect health, chemoprevention, breast cancer, metastatic breast cancer, death, endometrial cancer, pulmonary emboli, cataract surgery, and hip fracture from osteoporosis.

**Study designs and other criteria for inclusion in the review**
One of the studies used to derive the effectiveness evidence was the Breast Cancer Prevention Trial. The main study, which was used to derive the utility weights used to calculate quality-adjusted survival, involved healthy women aged 33 to 50 years and was based on the time-trade-off questionnaire. Details of the design of the remaining primary studies were not reported.

**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**
The effectiveness evidence was obtained from eight primary studies.

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

**Investigation of differences between primary studies**
Not stated.
Results of the review
For tamoxifen (t) and placebo (p), the incidence rates of invasive breast cancer were:

3.77(t) and 6.70(p) in age class 35 - 49, 3.10(t) and 6.28(p) in age class 50 - 59, and 3.33(t) and 7.33(p) in age class 60 or over;

1.43(t) and 10.11(p) in group 1, 5.69(t) and 12.99(p) in group 2, 4.52(t) and 13.28(p) in group 3, and 4.75(t) and 8.68(p) in group 4.

The incidence rates for other outcomes were 0.06(t) and 0.18(p) for non-invasive breast cancer, 3.05(t) and 0.76(p) for endometrial cancer, 1(t) and 0.31(p) for pulmonary embolism, 24.82(t) and 21.72(p) for cataracts, and 0.46(t) and 0.84(p) for hip fracture.

The mortality rates were not reported.

At diagnosis, 70% of women had stage I disease and 30% of women had stage II disease. ER status had no effect on survival.

Women could independently develop more than one outcome, and this risk was randomly distributed in each group.

The duration of tamoxifen benefit was 5 years.

The utility values were 1 for perfect health, 0.79 for chemoprevention, 0.68 for breast cancer, 0.52 for metastatic breast cancer, 0 for death, 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 some assumptions used in the decision model.

Estimates of effectiveness and key assumptions
It was assumed that:

patients developing endometrial cancer, thromboembolism/pulmonary embolism or cataracts while taking tamoxifen would immediately discontinue the treatment;

the risk for such conditions was elevated only during treatment;

women discontinuing tamoxifen would not experience any of its benefits thereafter;

women developing side effects had the same risk of breast cancer as other women;

women developing breast cancer while taking tamoxifen would have the same mortality risk as other women with breast cancer; and

women who died with breast cancer would have had metastatic disease for three years before death.

Measure of benefits used in the economic analysis
The benefit measures used in the economic analysis were survival and quality-adjusted survival. Both were derived using modelling. A 3% discount rate was used as the time horizon of the analysis was long. The quality weights used to calculate quality-adjusted survival were derived from published studies.

Direct costs
A 3% yearly discount rate was applied because the costs were incurred over more than two years. The unit costs were reported, but the quantities of resources were not clear. A detailed breakdown of the costs was provided. The health services included in the economic evaluation were care of women with and without cancer, and the treatment of complications. The cost/resource boundary adopted in the analysis appears to have been that of the third-party payer. The costs were estimated on the basis of wholesale drug prices for tamoxifen, Medicare reimbursement rates for the treatment of complications, and the Group Health Cooperative of Puget Sound for cancer care costs. No mention was made of the resource use data. All prices were given in 1998 values using the medical care component of the Consumer Price Index.

**Statistical analysis of costs**
Statistical analyses of the costs were not conducted.

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were conducted to evaluate the robustness of the estimated cost-effectiveness and cost-utility ratios to changes in the following model assumptions:

- the duration of tamoxifen benefit was varied to last 10 or 15 years rather than 5 years;
- after two years only 80% of women continued to take tamoxifen;
- higher or lower tamoxifen costs; and
- tamoxifen reduced the risk of hip fractures.

**Estimated benefits used in the economic analysis**
In group 1, estimated survival was 202 days in age class 35 - 49, 89 days in age class 50 - 59, and 45 days in age class 60 or over.

In group 2, estimated survival was 162 days in age class 35 - 49, 73 days in age class 50 - 59, and 38 days in age class 60 or over.

In group 3, estimated survival was 195 days in age class 35 - 49, 86 days in age class 50 - 59, and 43 days in age class 60 or over.

In group 4, estimated survival was 99 days in age class 35 - 49, 50 days in age class 50 - 59, and 28 days in age class 60 or over.

Gains in quality-adjusted survival were similar, but smaller in all groups (the data were only reported graphically).

**Cost results**
The estimated total costs were not reported.

**Synthesis of costs and benefits**
Incremental cost-effectiveness and cost-utility ratios were calculated to combine the costs and benefits of tamoxifen treatment to placebo.

In group 1, the incremental cost per life-year saved (LYS) was $8,845 in age class 35 - 49, $27,162 in age class 50 - 59, and $67,865 in age class 60 or over. The incremental costs per quality-adjusted life-year (QALY) were $9,777 (age 35 - 49), $26,990 (age 50 - 59) and $53,765 (age 60 or over), respectively.

In group 2, the incremental cost per LYS was $13,663 in age class 35 - 49, $35,984 in age class 50 - 59, and $81,126 in age class 60 or over. The incremental costs per QALY were $16,232 (age 35 - 49), $37,351 (age 50 - 59) and $68,334 (age 60 or over), respectively.

In group 3, the incremental cost per LYS was $9,371 in age class 35 - 49, $28,034 in age class 50 - 59, and $69,061 in age class 60 or over. The incremental costs per QALY were $10,818 (age 35 - 49), $27,901 (age 50 - 59) and $54,884 (age 60 or over), respectively.

In group 4, the incremental cost per LYS was $30,187 in age class 35 - 49, $64,654 in age class 50 - 59, and $120,091 in age class 60 or over. The incremental costs per QALY were $40,990 (age 35 - 49), $80,869 (age 50 - 59) and $127,750 (age 60 or over), respectively.

A further high-risk group was considered, a Gail model relative risk of greater than 1.6. For this group, the incremental cost per LYS was $48,364 in age class 35 - 49, $82,920 in age class 50 - 59, and $124,052 in age class 60 or over. The incremental costs per QALY were $79,320 (age 35 - 49), $122,519 (age 50 - 59) and $137,753 (age 60 or over), respectively.

The sensitivity analyses showed that a longer duration of tamoxifen generates improved the cost-effectiveness and cost-utility ratios in all patient groups. The price of tamoxifen had a great impact on the study results. Patients who started tamoxifen therapy at a younger age obtained the greatest benefit.

Authors' conclusions
Tamoxifen used in the primary prevention of breast cancer was cost-effective in high-risk women, especially those who started treatment at young ages.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Placebo was selected, as the aim of the study was to evaluate the active value of tamoxifen. Further, 'no primary prevention' represented the standard care in many settings. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness analysis used data derived from published studies. However, a formal review of the literature was not performed and the primary studies appear to have been combined using narrative methods. In addition, it was unclear whether the authors took into account the differences among the primary studies when estimating the effectiveness. Some assumptions were made to derive the effectiveness data used in the decision model. Most of these assumptions were based on published data. The authors investigated some, but not all, of the assumptions in the sensitivity analyses. This should be considered when interpreting the effectiveness results obtained.

Validity of estimate of measure of benefit
Survival and quality-adjusted survival were used as the benefit measures in the economic analysis. Both appear to have been appropriate and allow for comparisons to be made with the benefits of other interventions funded in the health care system. The quality weights were derived from a published study. Discounting was performed.

Validity of estimate of costs
The perspective adopted in the study appears to have been that of the third-party payer, although it was not explicitly stated. All the relevant categories of costs appear to have been included in the analysis. A detailed breakdown of the costs and their sources were reported, but resource consumption data were not given. The price year was reported, thus aiding reflation exercises to other settings. The cost estimates were specific to the study setting and no statistical analyses were conducted on the costs or quantities. However, the cost of tamoxifen was varied in the sensitivity analysis.

**Other issues**
The authors compared their findings with those from other studies. However, they did not address the issue of the generalisability of the study results to other settings. Although some sensitivity analyses were conducted, the overall external validity of the analysis was quite low. The study referred to women at high risk for breast cancer and this was reflected in the conclusions of the analysis.

**Implications of the study**
The authors pointed out that their findings "support targeting chemoprevention to those with the highest risk". Thus, tamoxifen should be the treatment of choice for women at risk of breast cancer. It is necessary to bear in mind that tamoxifen was compared to a placebo in this study, and not to any other equivalent drug.

**Source of funding**
Supported in part by grant no CRTG-98-260-01 from the American Cancer Society, Atlanta (GA), USA; the Sindab African American Breast Cancer Project, the Avon Breast Cancer Research and Care Program, and the Breast Cancer Alliance; and Cancer Center Support Grant no P30 CA13696-26 from the National Cancer Institute (NCI), Bethesda (MD), USA. D Hershman was the recipient of an NCI-funded postdoctoral fellowship (T32-CA09529).

**Bibliographic details**

**PubMedID**
11773148

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Anticarcinogenic Agents /adverse effects /economics /therapeutic use; Breast /pathology; Breast Neoplasms /drug therapy /economics /epidemiology /prevention & control; Carcinoma in Situ /drug therapy; Carcinoma, Lobular /drug therapy; Cost-Benefit Analysis; Decision Support Techniques; Drug Costs; Female; Humans; Hyperplasia /drug therapy; Markov Chains; Middle Aged; Quality-Adjusted Life Years; Risk; Tamoxifen /adverse effects /economics /therapeutic use

**AccessionNumber**
22002000232

**Date bibliographic record published**
31/10/2003

Date abstract record published
31/10/2003