Using prognostic information to select women with breast cancer for adjuvant systemic therapy

Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy

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Executive summary

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Executive summary

Background

During the second half of the twentieth century, researchers came to understand that breast cancer could spread to other parts of the body at an early stage in the development of the disease. This led to a large number of randomised trials testing the utility of adjuvant hormone and cytotoxic therapy. These trials have shown that adjuvant therapy reduces the risk of recurrence and death from breast cancer, such that combinations of modern hormonal and cytotoxic therapy might halve the risk of a woman dying of breast cancer in the first 10 years after diagnosis. However, these improvements in the outlook for women with breast cancer have – in the main – been achieved by research that has required the treatment of all patients, including those destined not to relapse and those who relapse despite adjuvant therapy. Because of this, researchers have sought to find prognostic and predictive factors which would allow patients most likely to benefit from adjuvant therapy to be identified. Using combinations of factors to develop prognostic models has further refined their use.

Objectives

The principal objective of this project was to investigate the cost-effectiveness of using prognostic information to identify patients with breast cancer who should receive adjuvant therapy.

Methods

This report systematically reviewed the literature on the prognostic and predictive factors in breast cancer. Health economic decision analytic modelling was then used to draw conclusions on the most effective and efficient use of these factors in selecting women with early breast cancer for adjuvant systemic therapy.

The size of the literature meant that it was not possible to review systematically all primary publications in the area. A series of systematic reviews and a survey were undertaken on the following topics:

- quality assessment of prognostic studies (not necessarily cancer)
- reviews of prognostic information in breast cancer
- prognostic models in breast cancer
- predictive factors in breast cancer
- the clinical use of prognostic information in breast cancer in the UK (survey)
- quality of life, cost and cost-effectiveness studies relevant to modelling.

Between six and nine databases were searched by an information expert. Evidence-based methods were used to review the abstracts, select those suitable for inclusion and extract the data using piloted data extraction forms for each of the systematic reviews. The quality of each included paper was assessed using standard assessment tools reported in the literature or piloted and developed for this study.

It was not possible to carry out a quantitative analysis of the data for any of the systematic reviews. Instead, narrative summaries of the evidence were prepared with commentaries on the strengths and weaknesses of the conclusions drawn.

A survey of clinical practice in UK cancer centres and units was carried out to ensure that conclusions drawn from the report could be implemented. These data, along with the information gathered in the systematic reviews, informed the methodological approach adopted for the health economic modelling. Estimation of a definitive model was not considered feasible based on the current published literature. Rather, given the obvious benefits to be gained by establishing prognosis and treatment effectiveness and cost-effectiveness for individual patients or groups of patients, a pragmatic decision was made to develop and report an illustrative framework for incorporating patient-level prediction within a health economic decision model. This framework was applied to a large retrospective dataset containing data on prognostic factors, treatments and outcomes for women with early breast cancer treated in Oxford. The data were used to estimate directly a parametric regression-based risk equation, from which a prognostic index was developed, and prognosis-specific estimates of the baseline breast cancer hazard could be ▶

observed. Published estimates of treatment effects, health service treatment costs and utilities were used to construct a decision analytic framework around this risk equation, thus enabling simulation of the effectiveness and cost-effectiveness of adjuvant therapy for all possible combinations of prognostic factors included in the model. Various ways of using the outputs from this framework were explored.

Results

Methodological quality of prognostic studies

There was a lack of empirical evidence to support the importance of particular study features affecting the reliability of findings and the avoidance of bias. However, there is much evidence that prognostic research in cancer tends to be of poor quality, contributing to the fact that prognostic markers often remain under investigation for years without good evidence that they are useful. Multiple small, separate, uncoordinated and often unvalidated studies often delay the process of defining the role of particular prognostic markers. Cooperation between research groups could lead to clear results emerging more rapidly, especially if such efforts are put into prospective studies or retrospective studies based on individual data from carefully assembled databases and/or tissue banks.

Systematic review of studies of prognostic factors

There is a plethora of evidence relating to possible prognostic factors for breast cancer. It was only possible to review those reviews that appeared to use systematic methods. There is a lack of high-quality, well-reported evidence in areas where it is taken for granted that factors have prognostic value, such as node status and age, and we have not reviewed these, accepting the commonly assumed value of such factors. A small number of eligible reviews (from 1 to –6 per factor) were found for each of 18 different factors. The lack of good-quality systematic reviews and well-conducted studies of prognostic factors in breast cancer was striking. In only five instances was the evidence strong enough to conclude that there is clear evidence of a relationship between the factor and survival (tumour size, proliferation indices, p53, cathepsin D and urokinase and its receptors).

Prognostic models

Although many prognostic models for breast cancer have been published, remarkably few have been re-examined by independent groups in independent settings. The few validation studies have been carried out on ill-defined samples, sometimes of smaller size and short follow-up, and sometimes using different patient outcomes when validating a model.

The evidence from the validation studies shows support for the prognostic value of the Nottingham Prognostic Index (NPI). No new prognostic factors have been shown to add substantially to those identified in the 1980s. Improvement of this index depends on finding factors that are as important as, but independent of, lymph node, stage and pathological grade. The NPI remains a useful clinical tool, although additional factors may enhance its use.

Predictive factors

We accepted that hormone receptor status (ER) for hormonal therapy such as tamoxifen and prediction of response to trastuzumab by HER2 did not require systematic review, as the mechanism of action of these drugs requires intact receptors. There was no clear evidence that other factors were useful predictors of response and survival.

Survey of UK practice when selecting women for adjuvant therapy

The survey confirmed pathological nodal status, tumour grade, tumour size and ER status as the most clinically important factors for consideration when selecting women with early breast cancer for adjuvant systemic therapy in the UK. The protocols revealed that although UK cancer centres appear to be using the same prognostic and predictive factors when selecting women to receive adjuvant therapy, much variation in clinical practice exists. Some centres use protocols based upon the NPI whereas others do not use a single index score. Within NPI and non-NPI users, between-centre variability exists in guidelines for women for whom the benefits are uncertain. Consensus amongst units appears to be greatest when selecting women for adjuvant hormone therapy with the decision based primarily upon ER or progesterone receptor (PR) status rather than combinations of a number of factors. Guidelines as to who should receive adjuvant chemotherapy, however, were found to be much less uniform.

Cost-effectiveness of prognostic models

Searches of the literature revealed only five published papers that had previously examined the cost-effectiveness of using prognostic information for clinical decision-making. ▶

These studies were of varying quality and highlight the fact that economic evaluation in this area appears still to be in its infancy.

By combining methodologies used in determining prognosis with those used in health economic evaluation, it was possible to illustrate an approach for simulating the effectiveness (survival and quality-adjusted survival) and the cost-effectiveness associated with the decision to treat individual women or groups of women with different prognostic characteristics.

The model showed that effectiveness and cost-effectiveness of adjuvant systemic therapy have the potential to vary substantially depending upon prognosis. For some women therapy may prove very effective and cost-effective, whereas for others it may actually prove detrimental (i.e. the reductions in health-related quality of life outweigh any survival benefit).

Conclusions and further research

Outputs from the framework constructed using the methods described here have the potential to be useful for clinicians, attempting to determine whether net benefits can be obtained from administering adjuvant therapy for any presenting woman; and also for policy makers, who must be able to determine the total costs and outcomes associated with different prognosis-based treatment protocols as compared with more conventional treat all or treat none policies. A risk table format enabling clinicians to look up a patient's prognostic factors to determine the likely benefits (survival and quality-adjusted survival) from administering therapy may be helpful. For policy makers, it was demonstrated that the model's output could be used to evaluate the cost-effectiveness of different treatment protocols based upon prognostic information. The framework should also be valuable in evaluating the likely impact and cost-effectiveness of new potential prognostic factors and adjuvant therapies.

Publication

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The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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The research reported in this monograph was commissioned by the HTA Programme as project number 98/36/02. The contractual start date was in May 2001. The draft report began editorial review in November 2002 and was accepted for publication in November 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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