Cost-effectiveness of raloxifene and hormone replacement therapy in postmenopausal women: impact of breast cancer risk

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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
Two alternative health technologies were assessed in the paper. The first was the use of hormone replacement therapy (HRT) in women with an intact uterus. This comprised 0.625 mg of an oral conjugated oestrogen per day with cyclic progestin for 10 to 14 days per month. The second was the use of raloxifene therapy (RT; 60 mg/day) in healthy 50-year-old postmenopausal women.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised healthy 50-year-old postmenopausal women.

Setting
The setting was the health service. The study was carried out in Philadelphia, PA, USA.

Dates to which data relate
The effectiveness data and cost data were derived from studies published from 1987 to 1999. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review of published studies.

Modelling
A time-dependent Markov model was used to simulate the outcomes of HRT, RT, or no therapy in hypothetical cohorts of 50-year-old healthy postmenopausal women. This included the six major outcomes affected by HRT and RT, which were coronary heart disease (CHD), vertebral fracture, hip fracture, thromboembolism, endometrial cancer and breast cancer. The authors stated that colon cancer and Alzheimer's disease were excluded due to the unavailability of data for the effects that HRT and RT have on these diseases. The risks of developing each outcome were independent of prior outcomes. The simulation was run until all cohort members died or reached an age of 101 years. All women were assumed to be compliant with therapy.

Outcomes assessed in the review
The outcomes assessed in the review were the transition probabilities for disease incidence and disease mortality of
CHD, hip fracture, vertebral fracture (which was assumed to affect the costs and quality of life, but not life expectancy), breast cancer, endometrial cancer, and thromboembolism. The relative risks of CHD, hip fracture, vertebral fracture, breast cancer, endometrial cancer and thromboembolism that postmenopausal women had under HRT or RT, were also assessed.

Study designs and other criteria for inclusion in the review
A variety of study designs were included in the review. For example, a prospective cohort study, randomised controlled trial, follow-up study, and population-based study. The authors did not state any inclusion or exclusion criteria for the studies considered in the review.

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
The authors reported some information to support the validity of the data within the model. In essence, a comparison between the life expectancy of a 50-year-old woman at average cardiac and breast cancer risk who selected no therapy from the simulation (31.68 years), and the estimated life expectancy of a 50-year-old US woman from the National Centre for Health Statistics (31.7 years).

Number of primary studies included
Seventeen primary studies were included in the review.

Methods of combining primary studies
The authors did not explicitly state the method used to combine the results of the individual primary studies. It would appear that they used a narrative method. However, some of the estimates were derived from a single study and no synthesis was therefore necessary.

Investigation of differences between primary studies
Not reported.

Results of the review
The transition probability for lifetime CHD incidence was 0.32. Its corresponding mortality was 0.1 to 0.3 for the first year that the event occurred, and 0.01 to 0.04 for subsequent years.

The transition probability for lifetime hip fracture incidence was 0.14. Its corresponding mortality was 0.17 for the first year.

The transition probability for lifetime vertebral fracture incidence was 0.18.

The transition probability for lifetime breast cancer incidence was 0.10. Its corresponding mortality was 0.025 for the first year and 0.032 for subsequent years.

The transition probability for lifetime endometrial cancer incidence was 0.026. Its corresponding mortality was 0.15 for the first year.
The transition probability for thromboembolism incidence was 0.00072 (annually). Its corresponding mortality for the first year was 0.016.

The relative risks of the six major outcomes within the model for postmenopausal women under HRT were CHD 0.56, hip fracture 0.53, vertebral fracture 0.53, breast cancer 1.35, endometrial cancer 1.00, and thromboembolism 2.10.

The corresponding values for postmenopausal women under RT were CHD 0.87, hip fracture 0.93, vertebral fracture 0.67, breast cancer 0.24, endometrial cancer 1.00, and thromboembolism 3.10.

Methods used to derive estimates of effectiveness
The estimates were derived from both the authors' assumptions and clinical expert opinion.

Estimates of effectiveness and key assumptions
The authors assumed the effect of HRT on vertebral fracture was the same as its effect on hip fractures. They also assumed that HRT did not increase the risk of endometrial cancer. The quality-adjusted life-years (QALYs) were calculated from utility values assigned to each health state in the model by 30 local internists (clinical expert opinion). The utility estimates were reported in full in the paper.

Measure of benefits used in the economic analysis
The measures of benefits used in the economic analysis were the life-years gained and QALYs gained.

The health benefits were discounted at a 3% annual rate to account for time effects, which was appropriate as they were obtained over a time period longer than 2 years. This discount rate is commonly used in studies performed in the USA. The benefits of therapies with a 5- or 10-year duration after menopause at age 50 were also analysed.

Direct costs
The resource quantities and the costs were not reported separately. The direct costs included in the analysis were those of the health service. These covered the average wholesale medication acquisition costs for HRT and RT, and the costs of medical care for health outcomes for the first year, subsequent years and death (due to CHD, hip fracture, vertebral fracture, breast cancer, endometrial cancer, and thromboembolism. These costs were included as input parameters in the Markov model. All the direct costs were obtained from the published literature. Although a societal perspective was adopted, the authors did not include the indirect medical costs or non-medical costs, due to the unavailability of these data.

The costs were discounted at a 3% annual rate as they were incurred over a time period longer than 2 years. This rate is consistent with that commonly used for other studies carried out in the USA. The price year was 2000. The medical component of the Consumer Price Index (2001) was used to adjust all the costs.

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

Indirect Costs
No indirect costs were reported.

Currency
US dollars ($).
Sensitivity analysis
One-way and two-way sensitivity analyses were conducted to assess the variability of the data and to provide information for women with different risk profiles. The sensitivity analyses conducted were very detailed, and were reported comprehensively in the paper.

Estimated benefits used in the economic analysis
Under long-term therapy, HRT increased life expectancy by 0.65 years when compared with no therapy, and increased the QALYs by 1.75. RT increased life expectancy by 0.71 years when compared with no therapy, and increased the QALYs by 1.32. When RT and HRT were compared, the increase in life expectancy produced by RT was 0.16 years. However, when the QALYs were considered as the measure of health benefit, RT decreased the QALYs by 0.43.

Under a 5-year therapy, 0.16 years of life expectancy were gained with HRT in comparison with no therapy, while the increase in QALYs was 0.45. When RT was compared with no therapy, the increase in life expectancy was 0.28 years, and the increase in QALYs was 0.52. The number of years gained by RT when compared with HRT was 0.12, and the increase in QALYs was 0.07.

Under a 10-year therapy, HRT resulted in 0.36 years more life expectancy than no therapy, and the increase in QALYs was 0.90. When RT was compared with no therapy, the increase in life expectancy was 0.47, while the QALYs gained were 1.03. When RT was compared with HRT, life expectancy increased by 0.11 years and the QALYs increased by 0.13.

Cost results
For a long-term therapy, the incremental cost was $3,802 for HRT and $12,968 for RT when compared with no therapy. The incremental cost of RT compared to HRT was $9,166.

For a 5-year therapy, the incremental cost was $2,259 for HRT and $4,851 for RT when compared with no therapy. The incremental cost of RT compared with HRT was $2,592.

For a 10-year therapy, the incremental cost was $3,834 for HRT and $8,123 for RT when compared with no therapy. The incremental cost of RT compared with HRT was $4,289.

Synthesis of costs and benefits
The incremental cost-effectiveness ratios were calculated as the cost per QALY gained with one therapy when compared with the other or with no therapy.

When a long-term therapy was considered, the cost per QALY gained was $2,173 for HRT compared with no therapy, and $9,824 for RT compared with no therapy. HRT was the dominant strategy when compared with RT, because it increased the number of QALYs gained (1.75 versus 1.32), at a lower cost ($3,802 versus $12,968).

For a 5-year therapy, the cost per QALY gained was $5,020 for HRT compared with no therapy, and $9,328 for RT compared with no therapy. RT was the most cost-effective strategy when compared with HRT, with a cost per QALY gained of $37,029.

For a 10-year therapy, the cost per QALY gained was $4,260 for HRT compared with no therapy, and $7,886 for RT compared with no therapy. RT was the most cost-effective strategy when compared with HRT, with a cost per QALY gained of $32,992.

Authors' conclusions
Long-term hormone replacement therapy (HRT) remains the dominant therapy for the majority of postmenopausal women without a major breast cancer risk factor, because it increases the quality-adjusted life expectancy at a lower cost. However, for postmenopausal women at significantly increased risk of breast cancer, long-term raloxifene therapy (RT) is the cost-effective therapy. It is also a cost-effective alternative for women with average breast cancer risk who
will not take HRT.

CRD COMMENTARY - Selection of comparators
The authors did not explicitly justify their choice of the comparator (no therapy), but this is a widely used comparator used in most cost-effectiveness analyses. The authors reported one limitation of their study. This concerned the fact that there were many other options for the prevention of osteoporosis, coronary disease and breast cancer, which have a single main effect. These might be even more effective than either HRT or RT for a specific complication of hormonal deficiency. However, the authors stated that to incorporate all of the available options would have made the analysis difficult to use.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. A narrative method appears to have been used to combine the estimates of effectiveness. The impact of differences between the primary studies on effectiveness was analysed through sensitivity analyses. As the authors stated, HRT and RT have side effects, but they found no evidence in the literature of differences in patient adherence to these therapies. The effectiveness analysis was conducted entirely on the assumption that the women were compliant with the therapies. However, this assumption was not justified, and there was no supporting evidence to show that the study population showed high rates of compliance.

Validity of estimate of measure of benefit
The estimation of benefits was modelled by applying utilities to the different health states in the Markov model. This seems to have been appropriate for the analysis. The authors reported that there were limitations concerning the fact that physician utilities were used as proxies for patient utilities. However, sensitivity analyses on the utilities showed no substantial change in the results obtained from the base-case analysis.

Validity of estimate of costs
The authors stated that although a societal perspective was consistent with the direct medical costs included in the analysis, some relevant outcomes (non-health effects and health effects on people other than the women undergoing therapy) and indirect costs could not be included due to the unavailability of data. The costs and the quantities were not reported separately. The date to which the prices related was reported.

Other issues
The authors made appropriate comparisons of their findings with those from other studies, but the issue of generalisability to other settings was not addressed. The authors reported that the available data were very limited, and this introduced uncertainty into the reliability of the conclusions. However, extensive sensitive analyses were used to analyse this uncertainty. Full and comprehensive results from the simulation were reported in the paper. The authors' conclusions appear justified within the limitations of the study.

Implications of the study
The authors highlight that there is a need for a large randomised controlled trial of HRT as primary prevention in order to facilitate decisions about postmenopausal therapy.

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Other publications of related interest


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