Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation

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
Preventive strategies for breast and ovarian cancer in women with BRCA1 or BRCA2 mutations at age 35 years were studied. The particular strategies examined were chemoprevention (tamoxifen for breast cancer and oral contraceptives for ovarian cancer), prophylactic surgery (bilateral salpingo-oophorectomy for ovarian cancer, and/or bilateral mastectomy for breast cancer) and surveillance. Surveillance included annual mammography, breast ultrasonography (if necessary), clinical breast examinations, and semi-annual gynaecology examinations, including pelvic examinations, ultrasonography, and CA-125 studies.

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 with BRCA1 or BRCA2 mutations.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
Most of the effectiveness data were obtained from studies published between 1983 and 2005. Some resource use data and costs were derived from studies and databases published from 1997 to 2006. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors' opinions.

Modelling
A Markov model with 25,000 Monte Carlo simulations was constructed to estimate the cost-effectiveness of the alternative strategies for women with a positive test result for BRCA1 or BRCA2 mutations. The model considered eight health outcomes: good health; death; breast cancer; ovarian cancer; both breast cancer and ovarian cancer; and side effects of oral contraceptives and tamoxifen, such as cataracts, endometrial cancer, and thrombophlebitis or pulmonary emboli. The cycle length was annual. In the base-case, women initiated their preventive strategy at 35 years of age, with up to 70 years of follow-up. A simplified version of the decision model structure was presented graphically.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the incidence of mutations, endometrial cancer due to tamoxifen, pulmonary embolism due to tamoxifen, and cataracts due to tamoxifen;

the cancer risk reduction due to the preventive strategies;

mortality associated with breast cancer, ovarian cancer, endometrial cancer, pulmonary embolism, or cataracts;

cancer stage distribution; and

utility values.

**Study designs and other criteria for inclusion in the review**

It was unclear whether a systematic review of the literature was undertaken to identify the primary studies. Only limited information on the design and other characteristics of the primary studies was provided. Cancer stage distributions were based on the Breast Cancer Prevention Trial. Mortality data were derived from US life tables and the Surveillance, Epidemiology, and End Results (SEER) Program. Utility values on cancer treatment-related and preventive treatment-related states were obtained from a study that used time trade-off ratings among women aged 33 to 50 years with a family history of breast cancer or with a personal history of several breast biopsies.

**Sources searched to identify primary studies**

Not reported.

**Criteria used to ensure the validity of primary studies**

The authors stated that their clinical assumptions were mainly based on observational studies because of the lack of clinical trials.

**Methods used to judge relevance and validity, and for extracting data**

Not reported.

**Number of primary studies included**

Clinical data were derived from 12 primary studies.

**Methods of combining primary studies**

A narrative approach appears to have been used to combine the primary estimates.

**Investigation of differences between primary studies**

Not reported.

**Results of the review**

The rate of incidence of BRCA1 mutation carriers per 100 persons per year was 3.32 (+/- 0.63) for breast cancer and 1.55 (+/- 0.304) for ovarian cancer. The rate of incidence of BRCA2 mutation carriers per 100 persons per year was 3.79 (+/- 1.07) for breast cancer and 0.523 (+/- 0.031) for ovarian cancer.

The rate of incidence per 100 persons per year was 0.401 (+/- 0.019) for endometrial cancer due to tamoxifen, 0.320 (+/- 0.180) for pulmonary embolism due to tamoxifen, and 0.110 (+/- 0.050) for cataracts due to tamoxifen.
The breast cancer risk reduction was 90% with prophylactic bilateral mastectomy, 95% with mastectomy and oophorectomy, 49% with tamoxifen, and 45% with oophorectomy before age 50 years.

The ovarian cancer risk reduction was 96% with oophorectomy and 54% with oral contraceptives.

The mortality rates for breast, ovarian and endometrial cancer and for pulmonary embolism and cataracts were age- and gender-specific.

Seventy per cent of women had localised (node-negative) cancer and 30% had regional (node-positive) cancer.

The utility values were:
0.77 (+/- 0.22) for breast cancer,
0.65 (+/- 0.21) for ovarian cancer,
0.76 (+/- 0.26) for prophylactic mastectomy,
0.81 (+/- 0.25) for chemoprevention,
0.82 (+/- 0.27) for prophylactic bilateral salpingo-oophorectomy,
0.73 (+/- 0.25) for both surgeries,
0.76 (+/- 0.29) for a health state of well with positive BRCA1 or BRCA2 test result,
0.68 for endometrial cancer,
0.50 for pulmonary emboli, and
0.68 for cataract surgery.

Methods used to derive estimates of effectiveness
The authors made some assumptions in the decision model.

Estimates of effectiveness and key assumptions
The risks of developing the two types of cancer were independent, while the risk reductions associated with the strategies under study lasted indefinitely.

Women had the same risk for cardiovascular disease and osteoporosis as that of the general population.

Women who experienced serious side effects from tamoxifen or oral contraceptives discontinued these treatments and thereafter used only surveillance as a strategy.

Measure of benefits used in the economic analysis
The summary benefit measures used were the life-years (LYs) gained and the quality-adjusted life-years (QALYs) gained. These were estimated using a modelling approach. An annual discount rate of 3% was applied. The utility weights were derived from the literature, as reported above. The lifetime risk for breast and ovarian cancer with each preventive strategy was also reported.

Direct costs
The analysis of the costs included only the direct medical costs. It appears to have been carried out from the perspective of the third-party payer. The categories of costs in the analysis were diagnosis of disease, preventive strategies,
treatment of cancer, treatment of side effects, and terminal care. The unit costs were presented for some items, while macro-categories of costs were given for others. The costs and some resource use data were estimated using data derived from Kaiser Permanente, Medicare payments, the Drug Topics Red Book, and some published studies. The total costs were estimated using the modelling approach. Discounting was relevant, as a lifetime horizon was chosen for the analysis, and an annual discount rate of 3% was applied. The costs were updated to 2004 values using the medical care component of the Consumer Price Index.

**Statistical analysis of costs**

The total costs were presented as mean values with standard deviations that were obtained from the Monte Carlo simulations.

**Indirect Costs**

The indirect costs were not included in the economic evaluations.

**Currency**

US dollars ($).

**Sensitivity analysis**

The decision model was based on a probabilistic analysis, thus all results were reported as means with standard deviation, to take into account the uncertainty in model parameters. Univariate sensitivity analyses were also carried out to assess the robustness of the base-case cost-effectiveness and cost-utility ratios to variations in some model assumptions, such as age at initiation of preventive strategies, lower reduction in cancer risk with tamoxifen, mortality rates, discount rates, costs, utility values and cancer incidence. Alternative values were presumably derived from published sources, although some values were set by the authors.

**Estimated benefits used in the economic analysis**

The expected LYs for women with BRCA1 mutation were 22.88 (+/- 0.59) with bilateral salpingo-oophorectomy, 23.65 (+/- 0.63) with mastectomy with bilateral salpingo-oophorectomy, 21.57 (+/- 0.53) with oral contraceptives, 21.55 (+/- 0.54) with tamoxifen, 21.07 (+/- 0.51) with surveillance, and 22.06 (+/- 0.56) with mastectomy.

The expected LYs for women with BRCA2 mutation were 22.90 (+/- 0.59) for bilateral salpingo-oophorectomy, 23.81 (+/- 0.63) for mastectomy with bilateral salpingo-oophorectomy, 22.29 (+/- 0.56) for tamoxifen, 21.89 (+/- 0.54) for oral contraceptives, 21.64 (+/- 0.53) for surveillance, and 23.01 (+/- 0.60) for mastectomy.

Mastectomy with bilateral salpingo-oophorectomy was thus the strategy that led to higher LYs gained for both BRCA1 and BRCA2 mutations.

The expected QALYs for women with BRCA1 mutation were 18.39 (+/- 2.69) with bilateral salpingo-oophorectomy, 17.44 (+/- 4.22) with mastectomy with bilateral salpingo-oophorectomy, 16.84 (+/- 1.39) with oral contraceptives, 16.75 (+/- 2.11) with tamoxifen, 15.64 (+/- 1.43) with surveillance, and 16.44 (+/- 2.92) with mastectomy.

The expected QALYs for women with BRCA2 mutation were 17.69 (+/- 3.62) for bilateral salpingo-oophorectomy, 18.36 (+/- 2.55) for mastectomy with bilateral salpingo-oophorectomy, 17.74 (+/- 2.50) for tamoxifen, 17.32 (+/- 1.40) for oral contraceptives, 16.42 (+/- 1.22) for surveillance, and 17.53 (+/- 3.41) for mastectomy.

Bilateral salpingo-oophorectomy alone was the strategy that led to higher QALYs for women with BRCA1 mutations, while mastectomy with bilateral salpingo-oophorectomy was associated with the highest QALYs gained for women with BRCA2 mutations.
Cost results
In the cost-effectiveness analysis, the expected lifetime costs for women with BRCA1 mutation were $119,058 with bilateral salpingo-oophorectomy, $120,869 with mastectomy with bilateral salpingo-oophorectomy, $130,205 with oral contraceptives, $135,130 with tamoxifen, $136,339 with surveillance, and $144,525 with mastectomy.

The expected costs for women with BRCA2 mutation were $116,186 for bilateral salpingo-oophorectomy, $116,227 for mastectomy with bilateral salpingo-oophorectomy, $121,735 for tamoxifen, $122,430 for oral contraceptives, $124,430 for surveillance, and $125,597 for mastectomy.

In the cost-utility analysis, the expected lifetime costs for women with BRCA1 mutation were $118,605 with bilateral salpingo-oophorectomy, $120,533 with mastectomy with bilateral salpingo-oophorectomy, $129,908 with oral contraceptives, $134,796 with tamoxifen, $135,858 with surveillance, and $144,295 with mastectomy.

The expected costs for women with BRCA2 mutation were $116,213 for bilateral salpingo-oophorectomy, $117,741 for mastectomy with bilateral salpingo-oophorectomy, $121,387 for tamoxifen, $122,153 for oral contraceptives, $124,016 for surveillance, and $125,477 for mastectomy.

Synthesis of costs and benefits
Incremental cost-effectiveness and cost-utility ratios were calculated in order to combine the costs and benefits. Strategies with lower LYs or QALYs and higher costs were dominated.

The incremental analysis revealed that, after excluding dominated alternatives, bilateral salpingo-oophorectomy was the reference strategy for women with BRCA1 mutation. The incremental cost per LY gained with mastectomy with bilateral salpingo-oophorectomy was $2,352. Bilateral salpingo-oophorectomy was also the reference strategy in the case of BRCA2. The incremental cost per LY gained with mastectomy with bilateral salpingo-oophorectomy was $100.

In the cost-utility approach, bilateral salpingo-oophorectomy was the reference strategy for BRCA1. It dominated all other preventive options. Bilateral salpingo-oophorectomy was also the reference strategy in the case of BRCA2. The incremental cost per QALY gained with mastectomy with bilateral salpingo-oophorectomy was $2,281. All the other strategies were dominated.

The sensitivity analysis showed that increasing the age at initiation of the preventive strategies did not change the order in terms of the cost-effectiveness found in the base-case analysis. However, the incremental cost-effectiveness ratios (for mastectomy with bilateral salpingo-oophorectomy compared with bilateral salpingo-oophorectomy alone) and cost-utility ratios (for bilateral salpingo-oophorectomy alone compared with mastectomy with bilateral salpingo-oophorectomy) increased at higher initiation ages. Changes in other model inputs did not affect the results of the analysis.

Authors’ conclusions
The most cost-effective strategies for women with positive test results for either a BRCA1 or a BRCA2 mutation were prophylactic bilateral salpingo-oophorectomy and prophylactic oophorectomy with mastectomy, respectively. Younger women benefited the most from the preventive strategies.

CRD COMMENTARY - Selection of comparators
The selection of the comparators appears to have been appropriate given the objective of the study. An exhaustive range of preventive measures was considered. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a synthesis of completed studies, which were presumably identified selectively. No details of the methods and conduct of a systematic review of the literature were given. The authors provided limited
information on the characteristics of the primary studies. For example, one of the studies was a clinical trial. However, as the authors pointed out, most of the primary sources were observational studies, which have a limited internal validity. Some assumptions were also made in order to populate the decision model. The impact of the changes in clinical estimates on the results of the analysis was comprehensively investigated in the probabilistic sensitivity analysis.

**Validity of estimate of measure of benefit**
The benefit measures used in the analysis were appropriate. QALYs capture the impact of the interventions on the most relevant dimensions of health (i.e. survival and quality of life). Further, both LYs and QALYs can be compared with the benefits of other health care interventions. Some utility weights were derived from a study that used the time trade-off method, a typical approach to elicit patient preferences for health states. Discounting was applied and the impact of changing the discount rate was investigated in the sensitivity analysis.

**Validity of estimate of costs**
The cost analysis was consistent with the perspective that appears to have been adopted in the study. Economic data (both unit costs and quantities of resources used) were derived from published sources such as administrative databases and some previous cost studies. However, limited information on such studies was provided. The unit costs were not presented separately from the quantities of resources used for some categories of costs, which might limit the possibility of replicating the analysis in other settings. However, the costs of cancer care were often presented as yearly macro-estimates. The total costs were modelled. The authors reported the price year, which will assist with reflation exercises in other time periods.

**Other issues**
The authors stated that their findings were consistent with those from other studies. The issue of the generalisability of the study results to other settings was implicitly addressed in the sensitivity analyses, where several model inputs were varied. The study referred to women with a BRCA1 or BRCA2 mutation and this was reflected in the authors' conclusions.

**Implications of the study**
The study results suggest that prophylactic bilateral salpingo-oophorectomy and prophylactic oophorectomy with mastectomy should be used, respectively, for women with BRCA1 and BRCA2 mutations.

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**Other publications of related interest**


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