Benefits and costs of screening Ashkenazi Jewish women for BRCA1 and BRCA2

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
Genetic screening of Ashkenazi Jewish women (a population with known high risk) for three specific BRCA 1/2 gene mutations. In the reference case, it was assumed that women were screened at age 30 and that the test was repeated for confirmation among women who tested positive. Four different prophylactic strategies were examined for positive cases: oophorectomy, mastectomy, oophorectomy and mastectomy, and surveillance alone.

Type of intervention
Screening and treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Ashkenazi Jewish women aged 30 to 80 years of age.

Setting
Genetic testing was assumed to take place in a genetic laboratory. All surgical procedures and treatments were assumed to take place in secondary care. The economic study was performed in the United States.

Dates to which data relate
Clinical probabilities were obtained from the literature published between 1995 and 1997. No dates were specified for the resource use data. 1995 prices were used.

Source of effectiveness data
The evidence for final outcomes was based on a review of previously completed studies and the assumptions of experts, using data on file from a genetic laboratory.

Modelling
A decision model of the costs and health effects associated with four alternative treatment strategies in BRCA1- and BRCA2-positive patients was used to assess the costs and benefits of screening a large high-risk population. Individuals were followed from age 30 to age 80 years using a Markov process.

Outcomes assessed in the review
The review assessed the risk of breast cancer and ovarian cancer by age 70, and reduction in the risk of developing cancer following prophylactic oophorectomy and mastectomy.
Study designs and other criteria for inclusion in the review
Data on the efficacy of prophylactic surgery were reported to be scarce and were derived from studies conducted before genetic testing was available.

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
One paper was cited for the evidence of the effectiveness of prophylactic oophorectomy and one paper was cited for the evidence for prophylactic mastectomy. The risks of breast cancer and ovarian cancer were based on a paper reporting the age-dependent cumulative probabilities of developing breast cancer and ovarian cancer in Ashkenazi Jewish women who tested positive for three specific mutations of BRCA1 and BRCA2.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The risk of breast cancer and ovarian cancer by age 70 were assigned the values of 56% and 16% in the reference case. The authors assumed that prophylactic oophorectomy would reduce the risk of developing ovarian cancer by 45% and that prophylactic mastectomy would reduce the risk of developing breast cancer by 90%.

Methods used to derive estimates of effectiveness
Estimates of effectiveness were also based on the authors' assumptions from data on file at Myriad Genetic Laboratories, Inc, Salt Lake City, UT.

Estimates of effectiveness and key assumptions
For the reference case, the authors assumed that the sensitivity of a single test for one of the three most common mutations among Ashkenazi Jewish women was 98% and that the specificity was 99%. The positive predictive value of the screening strategy in the reference case was 99.6% and the negative predictive value was 99.9% based on a mutation prevalence of 2.5% and a policy of considering the patient positive for this mutation only if two test results were positive.

Measure of benefits used in the economic analysis
Life years gained (increase in life expectancy days) and cancer deaths averted per 10,000 Ashkenazi Jewish women were used as the outcome measures in the economic analysis. Estimates of the age-dependent breast cancer-specific mortality were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results programme.

**Direct costs**
Costs were discounted. Quantities were not analysed separately from the costs. The authors assumed that gene testing for the three specific mutations found in patients of Ashkenazi Jewish ancestry would cost $450 using data on file at Myriad Genetic Laboratories. The cost of a full sequence analysis of BRCA1 and BRCA2 was assumed to be $2,400. A charge of $300 was included for genetic counselling. Estimates of other medical costs (screening, surgical procedures and treatment) were based on Medicare payments for 1995 from the Health Care Financing Administration. Drug costs for chemotherapy were obtained from the 1996 Fundamental Reference. The perspective adopted in the analysis was that of society. 1995 price data were used.

**Indirect Costs**
Not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way sensitivity analyses were performed to test the potential effects of each assumption on the model results. Monte Carlo simulations (a total of 2,000 simulations) were performed based on developing probability distributions on model parameters derived from the literature.

**Estimated benefits used in the economic analysis**
The incremental survival was estimated at 6 days (95% probability interval: 3 - 8) for surveillance, 11 days (4 - 25) for oophorectomy, 33 days (18 - 43) for mastectomy, and 38 days (22 - 57) for combined prophylactic mastectomy and oophorectomy. The number of discounted days added from combined surgery was 16 (7 - 31), from mastectomy was 13 (6 - 27), from oophorectomy was 4.49 (1 - 14) and from surveillance was 3 (1 - 5). Among 10,000 Ashkenazi Jewish women, screening at age 30 would avert 79 deaths from breast and ovarian cancer before age 80 if those who tested positive received both prophylactic mastectomy and oophorectomy. The corresponding values for surveillance, oophorectomy, and mastectomy were 2, 9, and 67.

**Cost results**
The discounted incremental cost for combined surgery compared with no screening was $900 (95% probability interval: 789 - 963), for mastectomy was $1,066 (1020 - 1145), for oophorectomy was $901 (830 - 964) and for surveillance was $988 (927 - 1,072). A 3% discount rate was used and in the sensitivity analyses the discount rate was varied from 2% to 4%.

**Synthesis of costs and benefits**
The median discounted incremental cost-effectiveness ratios ranged from $20,717 per life year for combined surgery to $134,273 for surveillance. The cost-effectiveness ratio was less than $50,000 per life-year in 98% of the simulations for combined surgery, 92% of the simulations for mastectomy, 28% of the simulations for oophorectomy, and none of the simulations for surveillance. The incremental cost was most influenced by the initial cost of the genetic test and counselling. The cost-effectiveness ratios of testing for those who tested positive and elected combined surgery would be $20,717 for the $450 test, $65,427 for the $2,400 test and only $14,869 for the $200 test.

**Authors' conclusions**
The model addressed the potential benefits and costs of genetic screening for this high-risk population and suggested
reasonable gains in survival at a reasonable cost, depending on the treatment strategies chosen, commensurate with the survival benefits and costs of currently accepted cancer screening strategies. Depending on current knowledge and the treatment strategies chosen, the analyses suggested that it may be reasonable and cost-effective to screen average-risk Ashkenazi Jewish women for BRCA1 and BRCA2 mutations.

CRD COMMENTARY - Selection of comparators
The reason for the choice of comparators (no screening) is clear.

Validity of estimate of measure of benefit
The internal validity of the estimates of the measures of benefits used in the economic analysis cannot be guaranteed due to the apparent lack of a comprehensive literature review and quality assessment of the primary studies included in the review, and also in view of the scarcity of data on the efficacy of prophylactic surgery (as noted by the authors).

Validity of estimate of costs
Resource quantities were not reported separately from prices. Adequate details of the methods of cost estimation were given. Although it was stated that a societal perspective had been adopted in the economic analysis indirect costs related to loss of productivity were not included.

Other issues
Given the uncertainties in the data, the authors' conclusions were justified. The issue of generalisability to other settings or countries was addressed by performing an extensive set of sensitivity analyses and appropriate comparisons were made with other studies. As mentioned by the authors, a cost-utility approach may have been a more appropriate analytic framework in a context in which psychological, social, and economic stigmatising are involved. The authors assumed that the test would improve quality of life in the screened population as 97.5% of screened women would learn that they did not have a high-risk form of the gene. They further assumed that the 2.5% who tested positive would not be in worse condition emotionally than they were before.

Implications of the study
According to this model study, screening is cost-effective only if all women who test positive undergo prophylactic surgery. These estimates require confirmation through prospective observational studies and clinical trials.

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