Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging


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 study examined the addition of screening with contrast-enhanced breast magnetic resonance imaging (MRI) to annual mammography for the detection of breast cancer (BC) in women with inherited BRCA1 or BRCA2 mutations. Annual mammography was performed from ages 25 to 69 years. Different starting ages and different frequencies (semi-annual, annual, biennial) were investigated for MRI screening. Among the different starting ages, the age groups considered were 25 to 69 years, 30 to 69 years, 35 to 54, 59, 64 or 69 years, and 40 to 49 or 54 years.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 25-year-old BRCA1/2 mutation carriers who had no history of BC and who had not undergone prophylactic mastectomy or chemoprevention.

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

Dates to which data relate
The effectiveness data and other clinical data were derived from studies published between 1993 and 2005. The resource use data were derived from studies published between 2004 and 2005. The price year was 2005.

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

Modelling
A published continuous-time Monte Carlo simulation model that estimated the effect of screening mammography on BC mortality was modified in order to characterise BRCA1/2 mutation carriers, to include the tumour detection characteristics of mammography and MRI, and to incorporate costs. Screening-related outcomes were modelled by mathematically superimposing screening events onto the natural history of BC. Few other details of the decision model were reported.

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

- the incidence of breast and ovarian cancer,
- tumour characteristics at symptomatic detection in the absence of screening,
- the reduction in risk of BC death with adjuvant therapy,
- the proportion of patients undergoing mastectomy by age at diagnosis and type of mastectomy, and
- the health state utilities for several conditions.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify primary studies. Data on the distributions of detected tumour size and stage in BRCA1/2 mutation carriers for women not undergoing screening were obtained from the US Surveillance, Epidemiology and End Results (SEER) database. All-cause mortality was estimated from official US mortality databases. Details of the other studies were not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Seventeen primary studies provided the clinical evidence.

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 cumulative BC incidence by age 70 years was 65% for BRCA1 mutation carriers and 45% for BRCA2 mutation carriers.

The 10-year risk of second primary BC was 43.4% for BRCA1 mutation carriers and 34.6% for BRCA2 mutation carriers.

The cumulative ovarian cancer incidence by age 70 years was 39% (range: 10 to 55) for BRCA1 mutation carriers and 11% (range: 5 - 30) for BRCA2 mutation carriers.

The tumour grade distribution was 29% Grade I-II and 71% Grade III for BRCA1 mutation carriers, and 57% Grade I-II and 43% Grade III for BRCA2 mutation carriers.
The oestrogen receptor-positive proportion for BRCA1 mutation carriers was 18% for the age group 20 to 49 years, 22% for the age group 50 to 69 years, and 24% for ages 70 years and older.

The oestrogen receptor-positive proportion for BRCA2 mutation carriers was 62% for the age group 20 to 49 years, 75% for the age group 50 to 69 years, and 83% for ages 70 years and older.

The tumour size for BRCA1 mutation carriers was less than 2 cm for 28%, 2 to 5 cm for 55%, and more than 5 cm for 17%.

The tumour size for BRCA2 mutation carriers was less than 2 cm for 32%, 2 to 5 cm for 54%, and more than 5 cm for 14%.

The tumour stage for BRCA1 mutation carriers was 45% local cancer, 48% regional cancer and 7% distant cancer.

The tumour stage for BRCA2 mutation carriers was 47% local cancer, 46% regional cancer and 6% distant cancer.

The mean tumour volume doubling time was 5.7 months (range: 3 to 8) for BRCA1 mutation carriers and 6.8 months (range: 3.7 to 10) for BRCA2 mutation carriers.

The median mammography tumour size detection threshold was 1.0 cm.

The proportion of mammographic non-detectable tumours was 66% (range: 66 to 100) for women aged younger than 50 years and 30% (range: 0 to 30) for women aged 50 years and older.

The reduction in risk of BC death with chemotherapy was 47% for women aged younger than 50 years and 31% for women aged 50 years and older.

The reduction in the risk of BC death with tamoxifen (oestrogen receptor positive) was 31%.

The proportion of patients undergoing mastectomy at diagnosis was 40% for bilateral surgery and 60% for unilateral surgery at ages 25 to 49 years, and 50% for both surgeries at age 50 years and older.

The health utilities by age were 0.90 for ages younger than 25 years, 0.96 for ages 25 to 34 years, and 0.93 for ages 35 to 44 years.

### Methods used to derive estimates of effectiveness

The authors made some assumptions that were used in the decision model.

### Estimates of effectiveness and key assumptions

Some of the assumptions were as follows.

The effect of a background rate of prophylactic bilateral salpingo-oophorectomy was assumed to be incorporated into baseline BC incidence rates.

In the absence of screening and adjuvant therapy, BC survival for BRCA1/2 mutation carriers was assumed to be equivalent to BC survival for BC patients in the SEER database pre-dating the widespread use of mammography and adjuvant therapy.

The MRI tumour size detection threshold was 0.5 cm (range: 0.3 to 0.8).

The health utilities by age were 1.00 for age younger than 25 years, 0.96 for ages 25 to 34 years, and 0.93 for ages 35 to 44 years.
The health state utilities for BRCA1/2 mutation carriage and in the year after negative screening were 1.00 (range: 0.95 to 1).

The health utility in the week while waiting for a diagnosis from suspicious screening findings was 1.00 (range: 0.83 to 1).

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the number of quality-adjusted life-years (QALYs). This was calculated by combining life expectancy and utility weights using a modelling approach. Other model outputs, including programme sensitivity, programme specificity, lead time, proportion of overdiagnosed cases, life expectancy and BC mortality reduction, were also estimated. An annual discount rate of 3% was used.

**Direct costs**
The analysis of the costs was carried out from a societal perspective. It included the direct medical costs of screening (and related procedures) and treatment of cancer. A detailed breakdown of the cost items was reported. The unit costs were presented separately from the quantities of resources used. The resource use data were derived from studies published between 2004 and 2005 and authors’ opinions. The costs of screening and related procedures were obtained using Medicare reimbursement rates, while the costs of cancer care were derived from published studies. Discounting was relevant, as long-term costs were evaluated, and an annual rate of 3% was used. The price year was 2005.

**Statistical analysis of costs**
Statistical analyses of the costs were not carried out.

**Indirect Costs**
The indirect costs (i.e. time lost from work) were included in the analysis, which was appropriate as a societal perspective was chosen. The unit costs and the quantities of resources used were presented separately. The costs were based on average salaries for women in 2005 and were derived from the US Bureau of Labor Statistics. Resource consumption was mainly derived from authors’ opinions and some published information. The price year was 2005. An annual discount rate of 3% was applied.

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate and multivariate sensitivity analyses were carried out to assess the robustness of cost-effectiveness ratios to variations in key model inputs using ranges of values derived from the literature. Alternative MRI frequencies, different BC risks and different age groups were also evaluated.

**Estimated benefits used in the economic analysis**
For BRCA1 mutation carriers, adding MRI to mammography alone increased the sensitivity of annual screening from 35 to 85%, the proportion of axillary lymph-node negative cancers from 57 to 81%, the mean lead time from approximately 1.5 to 3 years, and the false-positive rate from approximately 5 to 25%.

For BRCA2 mutation carriers, adding MRI to mammography alone increased the sensitivity of annual screening from 42 to 88%, the proportion of axillary lymph-node negative cancers from 61 to 81%, and the mean lead time from approximately 1.7 to 3.3 years.

With MRI, life expectancy increased from 71.2 to 73.3 years for BRCA1 mutation carriers and from 78.2 to 79.6 years.
for BRCA2 mutation carriers.

For both BRCA1 and BRCA2 mutation carriers, adding MRI reduced breast cancer mortality by 23% over that obtained from mammography alone.

For BRCA1 mutation carriers, the expected QALYs were 21.398 with no screening, 21.565 with mammography only, and ranged from 21.710 (age group 40 to 49 years) to 21.873 (age group 25 to 69 years) with mammography plus MRI by age.

For BRCA2 mutation carriers, the expected QALYs were 23.318 with no screening, 23.431 with mammography only, and ranged from 23.492 (age group 40 to 49 years) to 23.589 (age group 25 to 69 years) with mammography plus MRI by age.

Earlier starting ages and longer screening periods led to higher QALY gains for mammography plus MRI, as expected.

Cost results
For BRCA1 mutation carriers, the expected costs were $56,667 with no screening, $59,826 with mammography only, and ranged from $66,145 (age group 40 to 49 years) to $87,147 (age group 25 to 69 years) with mammography plus MRI by age.

For BRCA2 mutation carriers, the expected costs were $28,778 with no screening, $31,989 with mammography only, and ranged from $38,806 (age group 40 to 49 years) to $61,594 (age group 25 to 69 years) with mammography plus MRI by age.

Earlier starting ages and longer screening periods led to higher costs for mammography plus MRI, as expected.

Synthesis of costs and benefits
Incremental cost-utility ratios were calculated to combine the costs and benefits of the alternative strategies.

Relative to screening with mammography alone, the cost of adding annual MRI from the ages of 25 to 69 years was $88,651 per QALY gained for BRCA1 mutation carriers and $188,034 per QALY gained for BRCA2 mutation carriers. Considering a specific age group (35 to 54 years), the cost per QALY gained by adding MRI was $55,420 for BRCA1 mutation carriers, $130,695 for BRCA2 mutation carriers, and $98,454 for BRCA2 mutation carriers who had mammographically dense breasts. In this patient group, biennial MRI screening was characterised by lower costs and QALYs and a slightly lower incremental cost per QALY compared with mammography alone. Semi-annual MRI screening was more effective but not cost-effective in comparison with annual MRI.

The incremental cost per QALY gained was calculated for all screening strategies that incorporated annual MRI as well as annual mammography on the basis of different age groups. Each strategy was compared with the next most effective intervention. The cost per QALY gained ranged from less than $45,000 to more than $700,000, depending on the ages selected for MRI screening and the specific BRCA mutation.

The most relevant results of the sensitivity analysis were as follows:

MRI became more cost-effective as BC risk increased and less cost-effective as the risk decreased;

MRI screening became more cost-effective as the performance of mammography decreased;

the cost per QALY gained with MRI for BRCA1 and BRCA2 mutation carriers declined in proportion to reductions in the cost of MRI;

changes in the discount rates affected more life expectancy than costs;

if the utility value associated with the reassurance of a negative MRI increased, then the cost-effectiveness of MRI
improved significantly, especially among BRCA2 mutation carriers; BC risk was a key factor.

Authors’ conclusions
The addition of magnetic resonance imaging (MRI) to mammography in BRCA1/2 mutation carriers might be cost-effective, although the cost-effectiveness of the screening varied greatly by age. In general, MRI screening was more cost-effective for BRCA1 than BRCA2 mutation carriers. Even among BRCA1 mutation carriers, annual MRI screening was not cost-effective among younger women (aged 25 to 34 years) because of their lower incidence of breast cancer (BC), and among older women (aged over 55 years) because of declining quality of life and competing risk of death from other causes.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator (i.e. mammography alone) was appropriate as it represented the current screening strategy for women at risk of BC. The no-screening option was included mainly for comparative purposes. Different age groups for starting MRI screening were considered. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
Details of the method and conduct of a systematic review of the literature were not reported. The effectiveness evidence might, therefore, have been derived from selectively identified studies. With the exception of the SEER database, there was limited information on the studies used to estimate the clinical inputs. Consequently, it was difficult to determine the validity of the primary studies. Further, the authors made some assumptions because of the lack of published evidence or because of the uncertainty in some data. The issue of variability in the data was addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
QALYs were the most appropriate benefit measure because they capture the impact of the intervention on both quality of life and survival, which are the most relevant dimensions of health. The instrument used to derive utility was not explicitly reported. The utility weights were derived mainly from patients. Population-based estimates were also used. The use of QALYs enables comparisons with the benefits of other health care interventions. Discounting was applied, as recommended by guidelines for economic evaluations in the USA.

Validity of estimate of costs
The analysis of the costs was consistent with the societal perspective of the study, which was appropriate given that all potentially relevant costs were taken into consideration. The sources of the costs were reported for all items. The unit costs were presented separately from the quantities of resources used, which enhances the possibility of replicating the analysis in other settings. The authors investigated the issue of variability in the cost estimates. Statistical analyses of the costs were not performed. The price year was reported, which will facilitate reflation exercises in other time periods.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. However, extensive sensitivity analyses were carried out and alternative scenarios were considered. This increases the external validity of the analysis. The study referred to BRCA1/2 mutation carriers and this was reflected in the authors’ conclusions. The authors noted that the model could not account for all factors influencing the cost-effectiveness of MRI, such as the use of several chemoprevention agents and the use of breast conserving therapy.
Implications of the study
The study results suggested that the addition of MRI to mammography for detecting BC in BRCA1/2 mutation carriers might be cost-effective under specific conditions.

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