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Cost-effectiveness and comparative effectiveness of cancer risk management strategies in *BRCA1/2* mutation carriers: a systematic review

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Purpose: To review the evidence for the effectiveness and cost-effectiveness of cancer risk management interventions for *BRCA* carriers.

Methods: Comparative effectiveness and cost-effectiveness analyses were identified by searching scientific and health economic databases. Eligible studies modeled the impact of a cancer risk management intervention in *BRCA* carriers on life expectancy (LE), cancer incidence, or quality-adjusted life years (QALYs), with or without costs.

Results: Twenty-six economic evaluations and eight comparative effectiveness analyses were included. Combined risk-reducing salpingo-oophorectomy and prophylactic mastectomy resulted in the greatest LE and was cost-effective in most analyses. Despite leading to increased LE and QALYs, combined mammography and breast magnetic resonance imaging (MRI) was less likely to be cost-effective than either mammography or MRI alone, particularly for women over 50 and *BRCA2* carriers. Variation in patient compliance to risk management interventions was incorporated in 11/34 studies with the remaining analyses assuming 100% adherence.

Conclusion: Prophylactic surgery and intensive breast screening are effective and cost-effective in models of *BRCA* carrier risk management. Findings were based predominantly on assuming perfect adherence to recommendations without assessment of the health-care resource use and costs related to engaging patients and maximizing compliance, meaning the real-world impact on clinical outcomes and resource use remains unclear.

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Key Words: *BRCA*; breast cancer; cancer risk management; cost-effectiveness; ovarian cancer

INTRODUCTION

Women who inherit a pathogenic mutation in the *BRCA1* or *BRCA2* cancer-predisposing genes have a significantly elevated lifetime risk of breast and ovarian cancer, at 61–79% and 11–53% respectively.[1] *BRCA*-associated breast cancers are also more likely to be high grade with a younger age at onset.[2] Mutation carriers can mitigate their increased risk through risk-reducing surgery or intensive breast cancer screening for early detection.[3,4] While annual breast magnetic resonance imaging (MRI) and mammography lead to an earlier stage at diagnosis, whether this translates to a survival benefit is uncertain, especially for *BRCA1* carriers.[5,6] *BRCA1*-related breast cancers are typically estrogen- and progesterone-receptor-negative and HER2-unamplified (triple-receptor-negative), and share prognostic features with sporadic triple-receptor-negative cases including an increased likelihood of early distant recurrence and a limited association between tumor size and nodal status.[6,7] Similarly, although bilateral prophylactic mastectomy (BPM) reduces breast cancer risk by 90–100% its impact on overall survival is unclear.[3,8]

Risk-reducing salpingo-oophorectomy (RRSO) significantly lowers ovarian cancer risk as well as mortality.[3] Early results suggested around a 50% decrease in breast cancer risk for *BRCA* carriers who undergo premenopausal RRSO, but more recent findings suggest any risk reduction is limited to *BRCA2* carriers only.[4,9] Despite the positive impact on cancer risk, the potential for long-term adverse effects associated with premature surgical menopause, such as cognitive dysfunction and osteoporosis, are still under investigation.[10,11] In the absence of empirical trial data, decision modeling is likely to make a significant contribution in assessing the extent to which an intervention such as RRSO is effective and cost-effective.

Decision modeling can predict long-term outcomes for interventions by collating and synthesizing available evidence and modeling hypothetical scenarios. It can therefore project expected outcomes for an intervention when randomized trials or long-term observational studies are not feasible. As health resources are finite and in high demand, costs can be included in decision models to establish whether an intervention is also cost-effective. This is often judged using

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the ratio of the difference in costs to the difference in health outcomes between two or more alternate interventions (the incremental cost-effectiveness ratio, ICER).[12] An intervention will likely be cost-effective if the ICER falls below a societally predetermined willingness-to-pay threshold. Chosen thresholds vary across jurisdictions and are the subject of ongoing debate with, for example, suggested amounts ranging from $50,000–$150,000 per quality-adjusted life year (QALY) gained in the United States to £20,000–£30,000 per QALY gained in the United Kingdom.[13,14] Adjustments to the model can be made in cases of weak or missing data to assess how sensitive the model is to this data, and whether inaccuracies would significantly impact the outcome.

The value of identifying *BRCA* carriers relies on the subsequent uptake and effectiveness of appropriate risk management strategies. Women with *BRCA* mutations need to make important choices of the appropriate management option at different times in their lives, whilst clinicians and health policy planners need to know which are the most effective and cost-effective risk management options. The aim of this study was to perform a systematic review of economic evaluations and comparative effectiveness decision models to summarize the current evidence on costs, health benefits, and the cost-effectiveness of cancer risk management strategies for *BRCA* carriers.

MATERIALS AND METHODS

The review was undertaken according to the PRISMA guidelines.[15] The study is registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42016047341).

Search strategy and study selection

A systematic literature search was conducted for studies published from 1966 to March 2016 on the following databases: MEDLINE, Embase, Scopus, EconLit, ProQuest, Trove, OpenGrey, Cochrane Library, the National Health Service Economic Evaluation Database, Cost-Effectiveness Analysis Registry, Health Technology Assessment Database, and Internet searching. The search strategy included key terms relating to *BRCA1* and *BRCA2*, heredity, breast or ovarian cancer, risk management, and decision modeling (**Supplementary Table S1** online).

Articles were screened independently by two reviewers (A. T. and L.P.). Eligible studies were full economic evaluations or comparative effectiveness models that satisfied the following criteria: (i) a target population of confirmed or potential *BRCA1* or *BRCA2* carriers; (ii) included any breast or ovarian cancer risk management intervention; (iii) outcomes were measured as costs, life years gained (LYG), QALYs, or ICER; and (iv) was available in English. Where a study was an expansion or revision of a previously published model within the same geographical setting either the most recent or detailed publication was selected. Any discrepancies regarding study inclusion were discussed and resolved by consensus.

Data extraction and quality assessment

Data were extracted by one reviewer using a standardized data extraction form (**Supplementary Table S2**). Critical appraisal of economic evaluations was performed using the *BMJ* reporting guidelines, an established checklist outlining the major points to be considered in reporting cost-effectiveness analyses.[16] Methodological quality of comparative effectiveness studies was evaluated using the Phillips 2004 checklist, as recommended by the Cochrane Collaboration.[17,18]

Data synthesis and analysis

Data were synthesized and analyzed using a narrative approach. All costs are reported in 2016 USD by inflating the original currency according to the World Bank consumer price index and conversion using purchasing power parities.[19,20]

RESULTS

Study selection

The search yielded 4,551 references, reduced to 2,504 after removing duplicates. After screening of titles and abstracts, 98 studies were selected for full-text review from which 30 fulfilled eligibility criteria (**Figure 1**). Four additional references were added from an updated literature search performed on 21 July 2017.[21–24]

Description of studies: key characteristics

Eligible studies consisted of 8 comparative effectiveness analyses (CEs) and 26 economic evaluations (EEs), including five government-sponsored health technology assessments. Key characteristics are reported in Table 1 and **Supplementary Table S3**. Geographical settings were limited to a small selection of countries and predominantly based in the United States (16/34) (refs. 24–39) or United Kingdom (7/34) (refs. 21,40–45). Only three studies directly used clinical data obtained either through trial-based analyses or local databases,[41,45,46] with the majority using hypothetical simulations with inputs either from the literature or based on expert opinion. Target populations were exclusively female. From the EEs, 12/26 assessed the cost-effectiveness of breast cancer screening,[6,22,26,32,37,40,41,44,45,47–49] 2/26 prophylactic surgery,[50,51] 4/26 a combination of risk management interventions,[23,24,27,39] and the remaining 8/26 were evaluations of genetic testing or cancer genetics services.[21,28–30,33,43,46,52] Risk-reducing medication was considered in only 4/34 studies.[27,31,34,43] Excluding studies reporting solely on *BRCA1* carriers, fewer than half (10/22 EEs, 1/7 CEs) analyzed and reported separate outcomes for *BRCA1* versus *BRCA2*,[24,26,27,32,35,40,41,44,48,50,52] although some did factor in weighted cancer risk estimates based on expected relative carrier proportions in the target population.[29,30,33,43,49]

Description of studies: quality assessment

EEs were generally of good quality, with 24/26 satisfying at least 80% of the 35 items in the *BMJ* checklist

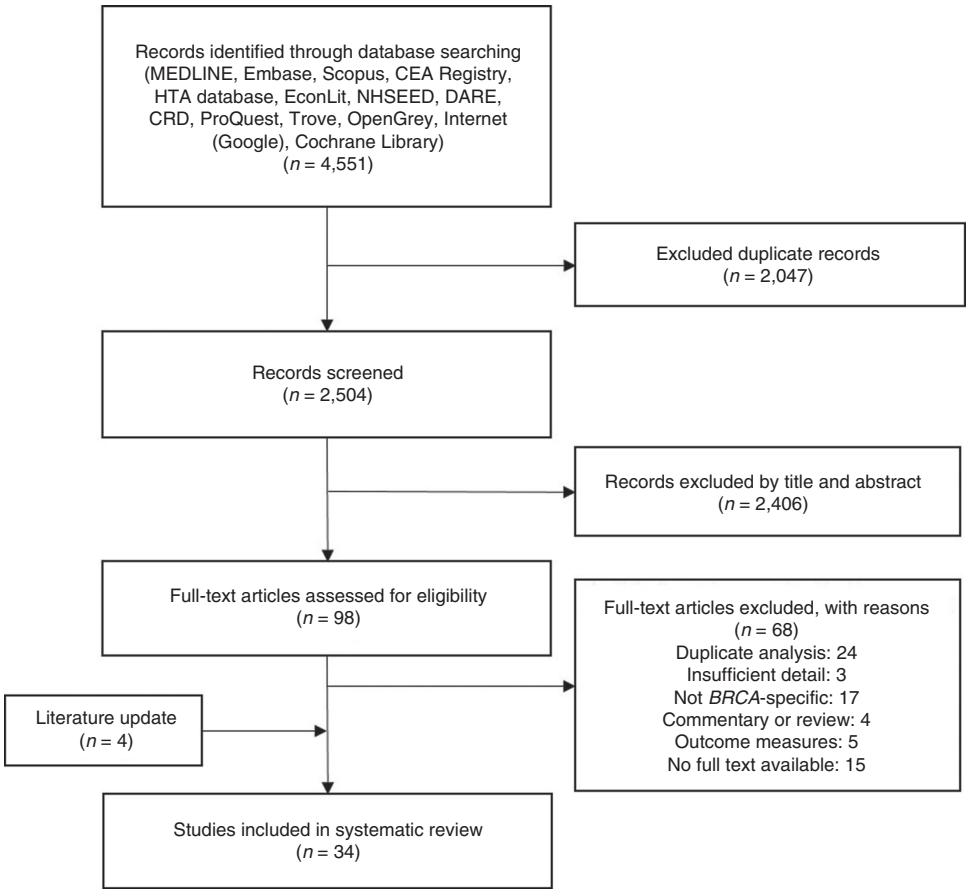

Figure 1 PRISMA flow diagram for study selection. CEA, Cost-Effectiveness Analysis Registry; CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; HTA, Health Technology Assessment Database; NHSEED, National Health Service Economic Evaluation Database.

(**Supplementary Table S4**). CE quality was more variable, ranging from 65 to 97%, primarily due to underreporting related to model uncertainty (**Supplementary Table S5**).

The viewpoint of the analysis was not expressly stated in 9/26 of EEs, although could usually be inferred from the description of costs included.[26,27,33,40,43,46,47,52,53] Other areas that were inadequately reported were details of price adjustments to account for inflation or currency conversion (15/26),[21–23,29,30,32,33,39,41,44,45,47,49,50,53] and justification for the specific costs included in studies that measured productivity changes such as lost wages (2/6).[32,51] Model inputs for cancer penetrance, mortality, and the clinical effectiveness of interventions were clearly stated. For studies using multiple sources, the method of selection and synthesis of effectiveness estimates were often poorly reported or unclear (10/15).[23,26,27,32,33,37,40,44,50,52] Sensitivity analyses were of mixed quality; a probabilistic sensitivity analysis was performed in 11/34 studies,[21,23,24,27,28,40,43–45,48,49] and 13/34 reported a more limited one-way sensitivity analysis only.[22,30,31,33,35,37,39,41,46,47,51,52,54]

BRCA-specific cancer survival was included in 12/34 studies.[24,29,30,32,38,43–45,47,50,51,54] These inputs were predominantly based on published data, with the exception of the earlier National Institute for Health and Care Excellence (NICE) analysis where poorer survival estimates for *BRCA1* carriers was based on expert opinion, and also dependent on the number of false-negative breast screens prior to diagnosis.[45] The same approach was adopted by two subsequent studies that expanded on the NICE model.[44,47] Intervention effects could not be directly linked to mortality due to a paucity of long-term data in *BRCA* carriers. Instead, surrogate outcomes such as an earlier stage at diagnosis for screen-detected cancers were assumed to lead to improved survival based on stage-specific cancer mortality rates from sporadic cancers in the general population. The lack of evidence for a survival benefit from breast screening was cited by three studies as the reason for not including mammography and/or MRI.[29,33,51]

A third of studies considered costs or health outcomes stemming from adverse effects of risk management interventions (6/26 EE, 4/8 CE). Several accounted for the radiation risk from mammography,[22,40,42,44,45,47,48] while others included risks associated with tamoxifen[27,34] or RRSO[25,34,50] such as endometrial cancer and cardiovascular disease. Selected studies indirectly accounted for adverse effects on health outcomes through reduced quality of life following events such as prophylactic surgery[21,23,28–31] or false-positive screening tests.[45,48]

Table 1 Study characteristics

Study	Setting	Analysis type	Intervention	Gene	Population[a]	Cancer	Outcomes
Armstrong et al.[25]	USA	Comparative effectiveness	Risk-reducing surgery	*BRCA1/2*	Confirmed carriers	Breast/ ovarian	LYG
Breheny et al.[52]	Australia	CEA	Genetic testing	*BRCA1/2*	FDR	Breast/ ovarian	Costs, cancer-free years
Cott Chubiz et al.[26]	USA	CUA	Screening	*BRCA1/2*	Confirmed carriers	Breast	Costs, LYG, QALYs
De Bock et al.[40]	UK, Netherlands	CEA	Screening	*BRCA1/2*	Confirmed carriers	Breast	Costs, LYG
Eccleston et al.[21]	UK	CUA	Genetic testing	*BRCA1/2*	Ovarian cancer patients and FDR/SDR	Breast/ ovarian	Costs, QALYs
Gamble et al.[24]	USA	CEA	Screening, risk-reducing surgery	*BRCA1/2*	Confirmed carriers (ovarian cancer affected)	Breast	Costs, LYG
Grann et al.[27]	USA	CEA and CUA	Screening, risk-reducing surgery	*BRCA1/2*	Confirmed carriers	Breast/ ovarian	Costs, LYG, QALYs
Griebsch et al.[41]	UK	CEA	Screening	*BRCA1/2*	Confirmed carriers	Breast	Costs, cancers detected
Griffith et al.[42]	UK	Comparative effectiveness	Cancer genetics service	*BRCA1/2*	Confirmed carriers	Breast	Costs, LYG, QALYs
HIQA et al.[48]	Ireland	CUA	Screening	*BRCA1/2*	Confirmed carriers	Breast	Costs, QALYs
Heimdal et al.[46]	Norway	CEA	Cancer genetics service	*BRCA1* founder	Breast/ovarian cancer patients and FDR	Breast	Costs, LYGs
Holland et al.[28]	USA	CUA	Genetic testing	*BRCA1/2*	Women with 10% carrier probability	Breast/ ovarian	Costs, QALYs
Kwon et al.[29]	USA	CEA and CUA	Genetic testing	*BRCA1/2*	Ovarian cancer patients and FDR	Breast/ ovarian	Costs, LYG, QALYs
Kwon et al.[30]	USA	CEA and CUA	Genetic testing	*BRCA1/2*	Breast cancer patients	Breast/ ovarian	Costs, LYG, QALYs
Kwon et al.[50]	Canada	CEA and CUA	Risk-reducing surgery	*BRCA1/2*	Confirmed carriers	Breast/ ovarian	Costs, LYG, QALYs
Manchanda et al.[43]	UK	CUA	Genetic testing	*BRCA1/2* Ashkenazi	Women of Ashkenazi descent	Breast/ ovarian	Costs, LYG, QALYs
Miller et al.[31]	USA	Comparative effectiveness	Genetic testing	*BRCA1/2* Ashkenazi	Women of Ashkenazi descent	Breast/ ovarian	LYG, QALYs
MSAC[47]	Australia	CUA	Screening	*BRCA1*	Confirmed carriers	Breast	Costs, LYG, QALYs
Muller et al.[23]	Germany	CEA and CUA	Screening, risk-reducing surgery	*BRCA1/2*	Confirmed carriers	Breast/ ovarian	Costs, LYG, QALYs
NICE[45]	UK	CUA	Screening	*BRCA1*	Confirmed carriers	Breast	Costs, QALYs
NICE[44]	UK	CUA	Screening	*BRCA1/2*	Confirmed carriers (breast cancer affected)	Breast	Costs, QALYs
Norum et al.[51]	Norway	CEA	Risk-reducing surgery	*BRCA1*	Confirmed carriers	Breast/ ovarian	Costs, LYG
Obdeijn et al.[22]	Netherlands	CEA	Screening	*BRCA1*	Confirmed carriers	Breast	Costs, LYG
Pataky et al.[49]	Canada	CUA	Screening	*BRCA1/2*	Confirmed carriers	Breast	Costs, QALYs
Plevritis et al.[32]	USA	CUA	Screening	*BRCA1/2*	Confirmed carriers	Breast	Costs, LYG, QALYs
Rijnsburger[53]	Netherlands	CEA	Screening	*BRCA1/2*	Confirmed carriers	Breast	Costs, LYG
Rubinstein et al.[33]	USA	CUA	Genetic testing	*BRCA1/2* Ashkenazi	Women of Ashkenazi descent	Ovarian	Costs, LYG, QALYs
Schrag et al.[34]	USA	Comparative effectiveness	Screening, risk-reducing surgery	*BRCA1/2*	Confirmed carriers (breast cancer affected)	Breast/ ovarian	LYG
Sigal et al.[35]	USA	Comparative effectiveness	Screening, risk-reducing surgery	*BRCA1/2*	Confirmed carriers	Breast/ ovarian	LYG

Table 1 Continued

Study	Setting	Analysis type	Intervention	Gene	Population[a]	Cancer	Outcomes
Sun[36]	USA	Comparative effectiveness	Screening, risk-reducing surgery	*BRCA1/2*	Confirmed carriers	Breast/ ovarian	LYG, QALYs
Taneja et al.[37]	USA	CUA	Screening	*BRCA1/2*	Confirmed carriers	Breast	Costs, LYG, QALYs
Tengs et al.[38]	USA	Comparative effectiveness	Genetic testing	*BRCA1/2*	Potential carriers (variable carrier probabilities)	Breast/ ovarian	LYG, QALYs
Van Roosmalen et al.[54]	Netherlands	Comparative effectiveness	Screening, risk-reducing surgery	*BRCA1*	Confirmed carriers	Breast/ ovarian	LYG, QALYs
Zendejas et al.[39]	USA	CUA	Screening, risk-reducing surgery	*BRCA1/2*	Confirmed carriers (breast cancer affected)	Breast	Costs, QALYs

CEA, cost-effectiveness analysis; CUA, cost–utility analysis; FDR, first-degree relative; HIQA, Health Information and Quality Authority (Ireland); LYG, life years gained; MSAC, Medical Services Advisory Committee (Australia); NICE, National Institute for Health and Care Excellence (UK); QALYs, quality-adjusted life years; SDR, second-degree relative.
[a]Target population unaffected by cancer unless otherwise specified.

The majority of studies assumed 100% uptake of risk management interventions (23/34).[22–27,31,32,34–41,44–49,54] Only 1 of the 18 breast screening studies accounted for a drop in attendance for subsequent screening rounds.[53] Variation in uptake of risk-reducing surgery was more widely modeled, with rates for the base case scenarios ranging from 20–52% for BPM to 50–88% for RRSO.[21,28–30,33,43,50,51]

Outcomes in confirmed *BRCA* carriers

Studies on unaffected women known to carry a *BRCA* mutation included 11/19 modeling breast screening, and 8/19 modeling risk-reducing surgery with or without a breast screening intervention pathway (Table 2). Screening studies were evenly divided between those broadly assessing breast MRI in addition to or instead of mammography,[27,37,41,44,45,47,49] and those focused on the optimal age intervals for combined mammography and MRI.[22,26,32,40,48,53]

Combined annual mammography and MRI was consistently the most effective screening strategy for the number of cancers detected, LYG, and QALYs. Estimates of the incremental cost-effectiveness for combined annual mammography and MRI varied widely, ranging between $19,837–$117,187 per LYG and $28,273–$236,644 per QALY gained when compared with either mammography or MRI alone. Extending the use of MRI alongside mammography beyond the age of 50 was less likely to be cost-effective.[26,27,32,40] The ICER was highly sensitive to cancer penetrance estimates meaning the addition of MRI was more likely to be cost-effective in younger rather than older women, and for *BRCA1* over *BRCA2* carriers.[26,32,40,47,48] Outcomes were also sensitive to the cost of MRI[26,27,32,37,41,45,49] and test performance.[22,26,32,48,49]

RRSO with BPM was associated with the greatest increase in life expectancy and the dominant strategy in terms of cost-effectiveness. It leads to an increase in life expectancy ranging from 1.29 to 9.0 LYG and 0.62 to 6.4 LYG compared with either no intervention[25,35,51] or cancer screening[23,27,35,36,54] respectively. Combined RRSO/BPM was less effective after adjusting for quality of life in 3/4 studies,[27,36,54] indicating that RRSO alone may be a cost-effective alternative with ICERs of $1,876 to $5,769 per QALY gained.[27] Inclusion of adverse effects related to RRSO-induced premature surgical menopause did not appear to affect results. One study further investigated this issue through a cost–utility analysis of risk-reducing bilateral salpingectomy with or without delayed oophorectomy as a speculative alternative to RRSO, as this approach has been suggested to minimize the potential long-term adverse effects associated with early RRSO.[50] Salpingectomy alone and salpingectomy with delayed oophorectomy were considered cost-effective alternatives for *BRCA1* carriers at $17,003 to $32,126 per QALY gained. They were potentially cost-effective for *BRCA2* carriers at $21,779 to $76,992 per QALY gained. Cost-effectiveness was highly sensitive to the disutility assigned to salpingectomy.

Three studies modeled interventions for *BRCA* carriers with a personal history of breast cancer,[34,39,44] and a fourth study included carriers recently diagnosed with ovarian cancer.[24] Following a primary breast cancer diagnosis, contralateral prophylactic mastectomy (CPM) with or without RRSO was the most effective for managing secondary breast cancer risk in terms of LYG and QALYs gained, and cost-saving when compared with breast cancer screening.[34,39] Combined annual mammography and MRI was the most effective of the intensive breast screening strategies, but comparison with the next most effective strategy of MRI alone resulted in ICERs unlikely to be acceptable at $195,340 to $257,467 per QALY gained.[44] In the case of breast cancer risk management after a diagnosis of ovarian cancer, BPM was only cost-effective in younger (aged 40–50) *BRCA1* carriers, and needed to be performed at least 5 years after the original ovarian cancer diagnosis.[24]

Outcomes in potential *BRCA* carriers

Several studies evaluated germ-line *BRCA* mutation testing alongside cancer risk management (Table 2). Genetic testing

Table 2 Effectiveness and cost-effectiveness outcomes for cancer risk management in *BRCA1/2* carriers

Study, country	Intervention[a]	Comparator	Gene	Incremental effectiveness			Total cost[b]	ICER[c]		
				LYG	QALY	Other[d]		LYG	QALY	Other[d]
Potential *BRCA* carriers										
Breheny, Australia[52]	Mammography or BPM age 38	No GT (breast)	*BRCA1*	—	—	+5.1	$5,489	—	—	$587
			BRCA2	—	—	+3.2	$5,260	—	—	$1,038
	RRSO age 40	No GT (ovarian)	*BRCA1*	—	—	+1.1	$2,870	—	—	$1,452
			BRCA2	—	—	+1.2	$2,805	—	—	$2,049
Eccleston, UK[21]	GT all ovarian cancers and FDR, with RRSO/ BPM/mammography/ MRI	No GT	*BRCA1/2*	—	+0.06	—	$20,010	—	$6,427	—
Griffith, UK[42]	RRSO and BPM age 35	No GT	*BRCA1/2*	+1.61	+0.0003	—	—	—	—	—
	RRSO age 35, mammography			+1.36	+1.67	—	—	—	—	—
Heimdal, Norway[46]	GT all breast/ovarian cases with mammography	Family history–based GT	*BRCA1* founder	+7.15	—	+0.3175	$13,244	$1,241	—	$27,942
Holland, USA[28]	BPM or RRSO age 35, or no surgery	No GT	*BRCA1/2*	—	+0.2	—	$140,040	—	$3,119	—
Kwon, USA[29]	GT all ovarian cancers and FDR, with RRSO/ BPM	GT all serous	*BRCA1/2*	+0.007	+0.007	—	$6,782	$177,721	$177,721	—
Kwon, USA[30]	GT all breast cancers diagnosed before 50, with RRSO/CPM	GT all triple-negative breast cancer diagnosed before 50	*BRCA1/2*	−0.003	+0.061	—	$7,542	*Dominated*	$62,153	—
Manchanda, UK[43]	Population-based GT with BPM/RRSO	Family history–based GT	*BRCA1/2*[e]	+0.025	+0.031	—	$2,737	Dominant	Dominant	—
Miller, USA[31]	RRSO age 40	Biennial mammography	*BRCA1/2*	+0.17	−1.26	—	—	—	—	—
	RRSO and BPM age 40			+0.95	−1.39	—	—	—	—	—
	Tamoxifen			−0.09	−0.7	—	—	—	—	—
Rubinstein, USA[33]	RRSO age 40	No GT	*BRCA1/2*[e]	+0.037	+0.046	—	$11,586	$11,840	$9,524	—
Confirmed *BRCA* carriers: breast screening										
Cott Chubiz, USA[26]	Alternating 6 monthly mammography/MRI age 30–70	Mammography	*BRCA1*	—	+0.12	—	$129,879	—	$82,550	—
			BRCA2	—	+0.06	—	$126,577	—	$236,644	—
De Bock, UK and Netherlands[40]	MRI age 25–30 mammography/MRI age 30–60 (Netherlands strategy)	Mammography/ MRI age 30–50 (UK strategy)	*BRCA1*	+0.257	—	—	$3,629	$4,584	—	—
			BRCA2	+0.154	—	—	$3,942	$8,220	—	—
Griebsch, UK[41]	MRI only from age 35	Mammography	*BRCA1*	—	—	+0.024	$624	—	—	$22,674
			BRCA2	—	—	+0.004	$613	—	—	$123,378
	Mammography/MRI from age 35	MRI	*BRCA1*	—	—	+0.0	$698	—	—	*Dominated*
			BRCA2	—	—	+0.016	$714	—	—	$6,162

Table 2 Continued

Study, country	Intervention[a]	Comparator	Gene	Incremental effectiveness			Total cost[b]	ICER[c]		
				LYG	QALY	Other[d]		LYG	QALY	Other[d]
HIQA, Ireland[48]	Mammography/MRI from age 30	MRI	*BRCA1*	—	−0.011	—	$14,074	—	*Dominated*	—
			BRCA2	—	−0.009	—	$12,027	—	*Dominated*	—
MSAC, Australia[47]	Mammography/MRI age 30–49	Mammography	*BRCA1/2*	+0.344	+0.264	—	$12,798	$19,837	$25,848	—
NICE, UK[45]	MRI age 30–39	Mammography	*BRCA1*	—	+0.137	—	$13,422	—	$24,437	—
	Mammography/MRI age 30–39	MRI		—	+0.03	—	$14,270	—	$28,273	—
NICE, UK[44]	MRI age 40–49	Mammography	*BRCA1*	—	+0.153	—	$7,486	—	$10,494	—
			BRCA2	—	+0.143	—	$7,085	—	$11,005	—
	Mammography/MRI age 40–49	MRI	*BRCA1*	—	+0.005	—	$8,462	—	$195,340	—
			BRCA2	—	+0.004	—	$8,114	—	$257,468	—
Obdeijn, Netherlands[22]	MRI age 25–60 mammography age 40–60	MRI age 25–60 mammography age 30–60	*BRCA1*	+0.002	—	—	$14,053	$342,105	—	—
Pataky, Canada[49]	Mammography/MRI age 30–64[f]	Mammography	*BRCA1/2*	—	+0.09	—	$8,954	—	$47,189	—
Plevritis, USA[32]	Mammography/MRI age 30–59	Mammography	*BRCA1*	+0.389	+0.284	—	$97,360	$61,275	$83,929	—
	Mammography/MRI age 35–59	Mammography	*BRCA2*	+0.164	+0.117	—	$58,532	$117,187	$164,262	—
Rijnsburger, Netherlands[53]	Mammography/MRI age 30–50	Mammography	*BRCA1/2*	+0.018	—	—	$2,737	$95,648	—	—
Taneja, USA[37]	Mammography/MRI age 40 (one exam only)	MRI	*BRCA1/2*	+0.0017	+0.002	—	$3,393	$39,041	$30,168	—
Confirmed *BRCA* carriers: risk-reducing surgery and combination strategies										
Armstrong, USA[25]	RRSO and BPM age 40 with HRT	RRSO age 40 without HRT	*BRCA1/2*	+2.77	—	—	—	—	—	—
Gamble, USA[24]	BPM 5 years after ovarian cancer diagnosis at age 50	Mammography/ MRI	*BRCA1*	+0.11	—	—	$166,059	$109,712	—	—
			BRCA2	+0.07	—	—	$179,283	$167,024	—	—
Grann, USA[27]	RRSO at 35 with MRI from age 30	RRSO and BPM age 35	*BRCA1*	−0.17	+0.02	—	$191,188	*Dominated*	$1,110,388	—
			BRCA2	−0.17	+0.072	—	$183,521	*Dominated*	$363,134	—
Kwon, Canada[50]	Salpingectomy age 40, oophorectomy age 50	RRSO	*BRCA1*	−0.324	+0.699	—	$32,426	*Dominated*	$14,838	—
			BRCA2	−0.483	+0.682		$28,134	*Dominated*	$20,183	
Norum, Norway[51]	RRSO at 35	No intervention	*BRCA1*	+3.1	—	—	$6,073	$1,959	—	—
	RRSO at 35 BPM at 30	RRSO		+3.3		—	$4,843	Dominant	—	—
Muller, Germany[23]	RRSO age 30	RRSO and BPM	*BRCA1/2*	−0.54	−0.95	—	$43,172	*Dominated*	*Dominated*	—
	Mammography/MRI			−2.21	−2.7	—	$56,418	*Dominated*	*Dominated*	—
Schrag, USA[34]	RRSO age 30	Mammography	*BRCA1/2*	+0.7	—	—	—	—	—	—
	RRSO and CPM age 30			+2.3	—	—	—	—	—	—
	Tamoxifen			+0.9	—	—	—	—	—	—

Table 2 Continued

Study, country	Intervention[a]	Comparator	Gene	Incremental effectiveness			Total cost[b]	ICER[c]		
				LYG	QALY	Other[d]		LYG	QALY	Other[d]
Sigal, USA[35]	RRSO age 40	Mammography/ MRI	*BRCA1*	+5	—	—	—	—	—	—
			BRCA2	+1.7	—	—	—	—	—	—
	RRSO and BPM age 40	from age 30	*BRCA1*	+6.4	—	—	—	—	—	—
			BRCA2	+2.4	—	—	—	—	—	—
Sun, USA[36]	RRSO age 30	Mammography and	*BRCA1/2*	+0.21	+0.6	—	—	—	—	—
	BPM age 30	ovarian cancer screening		+0.67	+1.0	—	—	—	—	—
	RRSO and BPM age 30			+0.94	+1.45	—	—	—	—	—
Van Roosmalen, Netherlands[55]	RRSO age 40, mammography from age 30	Mammography and ovarian cancer screening	*BRCA1*	+2.9	+3.0	—	—	—	—	—
	RRSO age 40, BPM age 30			+6.2	+3.4	—	—	—	—	—
Zendejas, USA[39]	CPM age 45	Mammography	*BRCA1/2*	—	+1.77	—	$43,360	—	Dominant	—

BPM, bilateral prophylactic mastectomy; CPM, contralateral prophylactic mastectomy; FDR, first degree relatives; GT, genetic testing; HIQA, Health Information and Quality Authority (Ireland); HRT, hormone replacement therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; MRI, magnetic resonance imaging; MSAC, Medical Services Advisory Committee (Australia); NICE, National Institute for Health and Care Excellence (UK); QALY, quality-adjusted life years gained; RRSO, risk-reducing salpingo-oophorectomy.
[a]Selected strategies only for most studies. All strategies for potential carriers include genetic testing in addition to the listed risk management interventions. All screening strategies are performed annually unless otherwise stated. [b]Costs are in 2016 USD inflated and converted from original currencies using the consumer price index and purchasing power parities. [c]Dominant refers to interventions that are both more effective and cost-saving to alternative compared. Dominated interventions are those that are less effective and more costly than the comparator. [d]Cancers detected or cancer-free years. [e]Ashkenazi founder mutations only. [f]Strategy also included MRI only for ages 25–29 and mammography only for ages 65–79.

strategies included: (i) testing of affected index cases with or without cascade testing of unaffected relatives,[21,29,30,46] (ii) family history or mutation prevalence-based approaches,[28,38,42,52] and (iii) target populations enriched for *BRCA* founder mutations.[31,33,43]

Four studies evaluated testing breast or ovarian cancer index cases with all but one including cascade testing of unaffected relatives and risk management interventions following a positive result. Two analyses of *BRCA* testing compared with no genetic testing for all ovarian cancer cases and their relatives produced very different ICERs of $6,427 (ref. 21) and $78,257 (ref. 29) per QALY gained. The impact of genetic testing on treatment decisions such as the use of poly ADP ribose polymerase inhibitors was not included, so no benefit for women already affected by ovarian cancer was captured in the model. The outcome was therefore highly sensitive to the number of predictive tests performed in unaffected relatives. Eccleston et al.[21] estimated an average of five relatives per index based on local clinic data, while Kwon et al.[29] modeled a single relative per index for the base case analysis leading to a substantially higher ICER. The cost-effectiveness of testing all ovarian cancer cases is also highly dependent on the reference strategy, as when compared with the next most comprehensive strategy of testing all serous ovarian cancers the ICER rose to $177,721 per QALY gained.[29] The third study limited testing of all breast and ovarian cancer cases to specific Norwegian *BRCA1* founder mutations at 0.6% prevalence, greatly reducing genetic testing costs and producing a result of $1,241 per LYG compared with family history-based testing.[46] Testing breast cancer index cases based on a young age at onset or triple-negative status is potentially cost-effective even when cascade testing of relatives is not modeled due to improved survival compared with ovarian cancer patients, and proven measures for secondary cancer prevention (CPM and RRSO).[30]

Another approach was to offer genetic testing with suitable risk management to unaffected women based on predefined mutation prevalence rates, such as 50% for relatives of known carriers. Compared with no genetic testing there were average gains of 0.45 QALYs and 1.1–5.1 cancer-free years when a woman has a 50% carrier probability,[38,52] and 0.055–0.69 QALYs for family history–based testing at 10–12% mutation prevalence.[28,38,42] Both EEs found genetic testing to be cost-effective at between $587 and $2,049 per cancer-free year[52] and $3,119 per QALY gained.[28]

The remaining analyses evaluated population-based *BRCA* founder mutation testing for individuals of Ashkenazi Jewish descent.[31,33,43] Population testing at 2.5% mutation prevalence was effective when paired with risk-reducing surgery or intensive screening with an additional 0.0369–1.29 LYG and 0.0459–0.3 QALYs gained compared with no genetic testing,[31,33] and 0.025 LYG and 0.031 QALYs gained

compared with family history–based testing.[43] Population-based testing was considered cost-effective against the current standard of family history–based testing by Rubinstein et al.[33] at $11,840/LYG and $9,524/QALY gained, and by Manchanda et al.[43] where it was both more effective and cost-saving. These results were based on similar uptake rates of RRSO in mutation-positive women (50% and 56%). The more favorable outcome from Manchanda et al. may be explained by the assumption of a 37–65% breast cancer risk reduction following RRSO, and the addition of BPM for 53% of the carriers identified.

DISCUSSION

The purpose of this systematic review was to collate existing evidence on the effectiveness and cost-effectiveness of cancer risk management strategies for *BRCA* mutation carriers. Prior systematic reviews have focused on evaluations of *BRCA* genetic testing strategies rather than the downstream consequences of identifying mutation carriers.[55–59] For studies including risk-reducing surgery the most effective strategy was usually the most cost-effective, whereas this did not necessarily apply to more intensive breast screening strategies due to higher costs over an extended period of time. Combined RRSO/BPM consistently resulted in the highest life expectancy, but not necessarily quality-adjusted life expectancy due to disutilities applied to undergoing both surgeries.[27,31,54] Annual MRI in addition to mammography was the most effective breast screening strategy in all but one case. The exception modeled active screening up until age 50 only, and reported that the combination of increased radiation dose and reduced mammographic sensitivity in younger women led to MRI alone being more effective.[48]

A major limiting factor across all studies is the lack of direct mortality data due to the absence of any conclusive longitudinal studies for *BRCA* risk management strategies. Reported survival with breast cancer screening was based on surrogate outcomes including stage at diagnosis,[26,27,48] tumor size,[35,40] estrogen receptor status,[26] and in some cases expert opinion.[44,45,47] Stage distributions for mammography- and MRI-detected cancers were obtained from clinical trial data, where adherence to screening is likely to be higher than within a clinical setting.[60] Consequently the use of stage-specific mortality estimates could bias results in favor of intensive screening. *BRCA1*-associated breast cancers are known to have distinct pathological features that are associated with poor prognosis in noncarriers, such as a high proportion of triple-negative cancers. Failure to account for these features could also skew results.[2,5] Ultimately it is not known whether these pathological features are prognostic in *BRCA1* carriers as the few studies reporting on breast cancer outcomes in this population have, in general, failed to detect a significant difference from noncarriers.[61]

Probabilistic sensitivity analysis and variation of methodological and structural assumptions are recommended for estimating the impact of parameter uncertainty and the robustness of study outcomes.[12] Areas of marked uncertainty include differences in patient uptake of risk management, and the impact of adverse effects. Variation in uptake was modeled in a third of studies. It was more likely to be included in evaluations of genetic testing and not in evaluations of the surgery or screening procedures themselves.[21,28–30,33,43,50–52] The cost-effectiveness of *BRCA* testing targeted at relatives of cancer-affected or founder mutation populations was dependent on reasonably high uptake of risk management strategies in mutation-positive women.[21,28–30,33,38,43,46,52] While published uptake rates of risk-reducing surgery and breast screening are typically high, uptake of risk-reducing medications such as tamoxifen or raloxifene is reported to be low across all settings.[62,63] This low uptake in clinical practice is reflected by very few studies actively considering the role of risk-reducing medication as a management strategy.

The valuation of quality of life for health states following an intervention or cancer diagnosis is a problematic area. Not considering the impact on quality of life can result in scenarios where invasive prophylactic surgery may be considered beneficial even in women at population risk of cancer. The source of utility valuations needs to be carefully considered, as utilities obtained from women at a population risk of cancer would likely not factor in an improvement in quality of life due to the reduction in cancer-related anxiety following prophylactic surgery.[64] In the case of *BRCA* carriers and known high-risk women, they tend towards assigning higher preference ratings for risk management interventions compared with women in the general population.[27,36] Only half of the studies addressed this by incorporating valuations obtained from either *BRCA* carriers[21,27,32,37,54] or women at high familial risk.[28–30,36,43,50,58]

There may be a significant length of time between a woman being informed of her mutation carrier status and her reaching a suitable age for an intervention such as RRSO, necessitating consideration of how to maintain engagement with mutation carriers to ensure they remain aware and participate in appropriate risk-reducing strategies. Only one EE reported consideration of resources and costs related to maximizing patient compliance through ongoing follow-up, whether in a community, hospital, or specialist clinic setting.[46] Several models assumed RRSO would be performed shortly after genetic testing between ages 30 and 35,[23,27,28,34,36,51,58] while reported uptake is on average up to 10 years later.[65] The potential long-term medical and psychological consequences of RRSO mean it is difficult to gauge the extent to which the benefit from reduction in ovarian cancer risk would be offset by an increase in other adverse health events during a woman's lifetime, particularly in women as young as 30. The relevance of assessing uncertainty in compliance rates, and also adverse events, ultimately depends on whether the model's aim is to predict outcomes relating to efficacy under ideal conditions, or instead to model effectiveness in a clinical practice setting as a decision-making tool.[66] By excluding consideration of these

uncertainties the resultant model could lead to overstating effectiveness and cost-effectiveness estimates.

The findings from these studies are likely to be context-specific due to the variability in target populations, health-care systems, and treatment pathways, together with a lack of transparency of underlying assumptions. While the studies are from a small selection of high-income Organisation for Economic Co-operation and Development countries, they feature a range of different health-care systems (public only, private, combined public and private), leading to potential differences in access and service delivery. In some cases established models are able to be adapted to different populations and jurisdictions, such as the MISCAN general breast screening microsimulation used by Rijnsburger.[53] Several studies were updates or variations of models reported previously, with adjustments made in light of new clinical data and changes in clinical practice.[26,27,35,40] Maximizing transferability is of interest as significant effort and resources go into developing models and cost-effectiveness analyses that resemble reality closely enough to assist in decision-making.

While all attempts were made to identify relevant publications there is a possibility relevant studies were missed, in particular non-peer-reviewed articles such as policy documents and commissioned reports, as well as studies not published in English or where full text was unavailable. Most studies had positive findings for intervention cost-effectiveness, indicating potential publication bias through exclusion of nonviable strategies prior to publication. As is common in systematic reviews of economic evaluations only a narrative summary was appropriate given the diversity in interventions included, study populations, and methodologies.[66]

This review identified numerous studies modeling the most effective or cost-effective approaches for cancer risk management in *BRCA* carriers, encompassing a range of variation in intervention pathways, timing, and adherence. Considering a single risk management intervention in isolation can be of theoretical interest, but the actual impact of *BRCA* carrier risk management can only truly be assessed by applying a combination of strategies across a woman's different life stages. Similarly, evaluations that include genetic testing should account for costs and benefits linked to notification of relatives who are eligible for cascade testing, due to its substantial impact on cost-effectiveness outcomes. For an accurate measure of cost-effectiveness further work is needed to model the costs and strategies involved in ensuring *BRCA* carriers comply with optimal risk management strategies over their lifetime. This requires considering the role of long-term high-risk cancer management programs and the health-care resources needed for ongoing follow-up of *BRCA* carriers, potentially extending many years past the initial receipt of genetic information.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

The authors declare no conflict of interest.

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