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Comparative effectiveness of screening and prevention strategies among *BRCA1/2*-affected mutation carriers

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Abstract

Comparative effectiveness research has become an integral part of health care planning in most developed countries. In a simulated cohort of women, aged 30–65, who tested positive for *BRCA1* or *BRCA2* mutations, we compared outcomes of mammography with and without MRI, prophylactic oophorectomy with and without mastectomy, mastectomy alone, and chemoprevention. Methods: Using Treeage 9.02 software, we developed Markov models with 25,000 Monte Carlo simulations and conducted probabilistic sensitivity analysis. We based mutation penetrance rates, breast and ovarian cancer incidence, and mortality rates, and costs in terms of 2009 dollars, on published studies and data from the Surveillance, Epidemiology, and End Results (SEER) Program and the Centers for Medicare and Medicaid Services. We used preference ratings obtained from mutation carriers and controls to adjust survival for quality of life (QALYs). Results: For *BRCA1* mutation carriers, prophylactic oophorectomy at $1,741 per QALY, was more cost effective than both surgeries and dominated all other interventions. For *BRCA2* carriers, prophylactic oophorectomy, at $4,587 per QALY, was more cost effective than both surgeries. Without quality adjustment, both mastectomy and BSO surgeries dominated all other interventions. In all simulations, preventive surgeries or chemoprevention dominated or were more cost effective than screening because screening modalities were costly. Conclusion: Our analysis suggested that among *BRCA1/2* mutation carriers, prophylactic surgery would dominate or be cost effective compared to chemoprevention and screening. Annual screening with MRI and mammography was the most effective strategy because it was associated with the longest quality-adjusted survival, but it was also very expensive.

Keywords

Comparative effectiveness; Cost-effectiveness; Mastectomy; Oophorectomy or both; Tamoxifen; Screening with MRI and mammography; *BRCA1/BRCA2*

Introduction

Among women with *BRCA1* or *BRCA2* genetic mutations, contrast-enhanced magnetic resonance imaging (MRI) combined with mammography has been recommended by the American Cancer Society and other authoritative groups for breast screening [1]. Many women who test positive for these mutations now choose to be followed with annual MRI combined with mammography rather than using chemopreventive agents or undergoing prophylactic mastectomy [2–6]. Although randomized trials have not been conducted, observational studies have found that prophylactic mastectomy and/or prophylactic bilateral salpingoophorectomy (BSO) can delay or prevent cancers of the breast and ovary among mutation carriers [7–10]. Mammography alone has not been found to be reliable enough for screening *BRCA* mutation carriers, in part, because they are at risk for breast cancer at much younger ages than non-carriers, and mammography does not accurately detect cancer in the dense breasts of young women. Recent observational studies have found that screening by MRI with mammography was effective in detecting earlystage breast cancers among *BRCA1/2* mutation carriers [11–15]. Currently, mutation carriers who have not been diagnosed with cancer may choose among or combine several preventive strategies: primary prevention with chemopreventive agents (e.g., tamoxifen), prophylactic mastectomy or prophylactic BSO; and secondary prevention with mammography and MRI [2, 16]. Comparative effectiveness analysis is increasingly being used to determine the relative merits of therapeutic interventions in specific patient populations. In a previous analysis, we showed that among mutation carriers, BSO with or without mastectomy was more cost effective than surveillance with annual mammograms [17–19]. Other analyses compared MRI with mammography to mammography alone and found that, although expensive,

limited use of MRI might be more cost effective than mammography [20–22]. Using recent cancer risk data on women with *BRCA1* and *BRCA2* mutations, we have now developed new models to estimate the comparative effectiveness, including quality-adjusted and unadjusted cost effectiveness, of the primary and secondary preventive interventions available to mutation carriers. For quality adjustment, we have used new preference ratings obtained from both women without known high risk and a Canadian cohort of BRCA1 or BRCA2 mutation carriers [23, 24].

Methods

We developed a Markov process [25] and used 25,000 Monte Carlo simulations with TreeAge ProSuite 2009 to estimate the survival, quality-adjusted survival, and costs associated with preventive interventions for *BRCA1* and *BRCA2* mutation carriers who had no cancer diagnosis at baseline [26]. The interventions (Fig. 1) were prophylactic mastectomy, prophylactic BSO, Prophylactic mastectomy and BSO (both surgeries), tamoxifen, mammography, mammography plus MRI (MRI), and prophylactic BSO plus MRI. (We assumed that women who had MRI would also have mammography because screening with both modalities is now the standard of care for women aged 30+ years, who have a *BRCA1/2* mutation [2].) In previous studies, we assumed that mammography alone was the standard of care. We chose five health states as outcomes: good health, breast cancer, ovarian cancer, both breast and ovarian cancer, their complications, and death. We used 25,000 simulations for the base case of this study and followed individuals for new primary breast and ovarian cancers from age 30 (base case) to 65 for survival. We assumed that women who had prophylactic surgery did so at age 35 and that all women started screening with MRI or mammogram at age 30 [27]. For each year of each strategy, we calculated the age-dependent probabilities of developing breast cancer, developing ovarian cancer, dying from breast or ovarian cancer, dying from any cause, or remaining well. We followed all women up to age 100 or death.

Health parameters

We included in our model published estimates of the cumulative incidence of breast cancer and ovarian cancer among *BRCA1/2*-positive women by decade [28]. We converted these 10-year risks to annual conditional probabilities of cancer, assuming constant instantaneous increases in incidence rates per year (Table 1) [19].

We assumed that among *BRCA1/2* mutation carriers, those with breast cancer had the same conditional probability of developing ovarian cancer as those who were well. Using the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program data for the period 1973–2004, we also computed estimates of dying with and without cancer [29]. Assuming that *BRCA1/2*-positive women who developed cancer would have the same conditional probability of death as women with cancer in the general population, we used SEER data to calculate the probabilities of dying [29]. We did not adjust our ovarian cancer survival estimates for screening because heightened surveillance does not appear to alter the prognosis of this cancer [30–32].

For women diagnosed with breast cancer, who were not being screened by MRI, we based our stage distribution assumptions on the cases among participants in the Breast Cancer Prevention Trial (BCPT). Of the BCPT participants in the control arm who developed breast cancer, 70% had localized (node-negative) and 30% regional (node-positive) disease [33].

We assumed that patients who had annual MRI screening would have the same stage distribution as the cases diagnosed in a cohort of 236 *BRCA1* and *BRCA2* mutation carriers, aged 25–65 years, who underwent annual MRI imaging, ultrasound, mammography, and

clinical breast examinations from November 3, 1997 to March 31, 2003 [2, 3, 14, 34 We applied to our model the distributions of pathological TNM stages, tumor size, lymph node status, grade, and hormone receptor status observed in their cancers [14, 35]. For both groups, we computed mortality risk based on SEER data for those distributions [29].

We updated our estimates of the health effects of preventive strategies to reflect the findings of studies published since our previous report. These studies suggest that prophylactic BSO may reduce the risk of ovarian cancer by 96% for *BRCA1* and *BRCA2* mutation carriers, respectively, and may reduce the risk of breast cancer among premenopausal women by 53% for both [8, 36, 37]. Other studies suggest that prophylactic bilateral mastectomy may reduce the risk of breast cancer by 90% [8]. Table 1 describes our risk assumptions. For our base case, the risk reductions associated with these strategies were assumed to last indefinitely.

We assumed that after prophylactic oophorectomy, most women would take hormone replacement therapy (HRT) until age 50, and that HRT would not affect their risks of breast cancer, cardiovascular disease, or osteoporosis [38].

Cost parameters

We obtained age-stratified data on screening and cancer care costs from the literature and expressed the costs in terms of 2009 US dollars (Table 2). Drug cost data were obtained from the Drug Topics Redbook: Pharmacy's Fundamental Reference [39]. Patient care costs associated with cancer were obtained from the literature and are given in terms of 2009 dollars.

Quality-of-life adjustment

We adjusted our survival estimates for quality of life based on preference ratings of cancer- and preventive treatment-related states obtained from both mutation carriers in the previously described MRI cohort and women without known high risk (Table 3) [14, 35, 40]. We interpreted the preferences of the latter group as representing a societal standard. The preference ratings were derived from responses to a time trade-off questionnaire, which presented vignettes or scenarios involving various cancer-related states and asked respondents how much of their life expectancy they would trade to avoid those states. The states were breast cancer, ovarian cancer, bilateral mastectomy, BSO, both surgeries, use of a chemopreventive medication (tamoxifen), mammography, and MRI. The cancer state vignettes quantified the risk of recurrence and the effect of the cancer on life expectancy. Each vignette was based on literature review, patient interviews, and professional oncological experience. The preference rating was calculated as total life expectancy minus traded time, divided by total life expectancy.

Comparative effectiveness analysis

We computed the mean cost (SD) of each intervention for a *BRCA1* or *BRCA2* mutation carrier to those who chose it. We then listed the interventions in the order of costs from the least to the most expensive. We computed the incremental cost of each intervention over that of the next most expensive one. We computed the mean survival (SD) in life years (LYs) or quality-adjusted life years (QALYs) associated with each intervention, and their incremental LYs or QALYs (positive or negative) above that associated with the least expensive intervention. Interventions that were more expensive and less effective (in LYs or QALYs) were designated as dominated. Extended dominance represents the percentage of the population that receives the less effective treatment and is considered dominated (Appendix Figure 4).

Results

Table 4 presents the results of the comparative effectiveness analyses, which we conducted separately for *BRCA1* and *BRCA2* mutation carriers. Based on the preferences of women without known high risk for breast or ovarian cancer, the optimal strategy for *BRCA1* mutation carriers was BSO, with an incremental cost effectiveness ratio (ICER) of $1,741 per QALY compared to both surgeries; for *BRCA2* mutation carriers, BSO had an ICER of $4,587(Table 4). With quality adjustment based on mutation carriers' preferences, the optimal strategy for *BRCA1* mutation carriers was still BSO, with an ICER of $1,677 per QALY. For *BRCA2* mutation carriers, prophylactic oophorectomy had extended dominance over bilateral mastectomy with an ICER of $4,535 per QALY (Table 4). MRI plus BSO was associated with the most QALYs of any strategy for *BRCA1* carriers, but at a cost of $170,899 and an unacceptable ICER of $736,788 per QALY compared to prophylactic oophorectomy alone.

Without quality adjustment, using LYs saved, the optimal strategy adopted for both *BRCA1* and *BRCA2* was prophylactic surgery, as it was the most effective and the least expensive (Table 4).

Mammogram versus MRI

In the United States, MRI costs nearly ten times as much as mammography alone (Table 2). If the cost of MRI among *BRCA1* carriers were reduced by 30% and that among *BRCA2* carriers by 10%, then MRI would be cost effective compared to mammography (Appendix Table 1). At a 70% cost reduction, MRI would dominate (i.e., would be less costly and would provide better survival than) mammography alone.

If penetrance approximated (Appendix: Table 2) the cancer incidence rates of women in the general population, mammograms would dominate MRI. If penetrance increased, then prophylactic surgery would dominate, but the benefit would differ according to *BRCA1* or *BRCA2* status.

Costs and effectiveness of our base case was 3%, but would decrease progressively in our sensitivity analysis (Appendix: Table 3) with an increase of 0–5% in the discount rates.

At all ages (Appendix: Table 4) among BRCA1 or BRCA2 carriers, both prophylactic surgeries would dominate other strategies in life years saved, but the benefit would decrease with quality adjustment.

Variability in both costs and effectiveness outcomes is demonstrated (Appendix: Figures 2 and 3) using 25,000 second-order probabilistic simulations of the rates. Annual MRI and mammography screening is more expensive and has greater quality-adjusted effectiveness compared to the five prevention strategies.

Discussion

To our knowledge, this is the first study conducted to analyze the comparative effectiveness of screening and primary prevention strategies among women who have tested positive for *BRCA1/2* mutations. For this analysis, we carefully followed guidelines on as to how to do the analysis as outlined by the American College of Physicians and Institute of Medicine [24]. The Congressional Budget Office may have had in mind such analyses of quality and cost [24, 41] in preparing its recent report submitted to health policy makers about the costs of suboptimal health care [42, 43]. Mutation carriers gave high preference ratings to MRI, but although it leads to the diagnosis of smaller cancers [2, 3], no randomized trial has

shown that it prolongs life [22, 44]. In short-term studies among younger women, it appears cost effective compared to mammography alone [20].

Before the widespread use of MRI, we conducted a cost-effectiveness analysis comparing genetic testing plus preventive surgical interventions with surveillance alone for *BRCA1/2* mutation carriers [19]. We showed that from a societal perspective, with unadjusted survival (LYs saved) as the outcome, *BRCA* testing followed by surgical intervention for those who tested positive was the most effective option.

In this study, we compared preventive surgery, chemoprevention, MRI, and mammography. Our outcomes were costs, life-years (survival), and quality-adjusted life-years. Quality adjustment takes into account the morbidity, emotional distress, and inconvenience that the preventive interventions entail [45, 46], which vary among individuals depending on their personalities and circumstances. As Table 3 indicates, mutation carriers and controls (women without known high risk) differed only slightly in their preference ratings [40]. Overall, study participants' preference ratings of each health state varied considerably, and our Monte Carlo simulations reflected this variation (Appendix: Figures 2 and 3). Quality adjustment had a tremendous impact on our cost-effectiveness estimates. The strategy of prophylactic mastectomy and oophorectomy had the lowest overall cost. It dominated all other strategies and had the longest survival in LYs, but the lowest preference ratings. These findings are similar to those reported in a recent study of an international group of 2,677 *BRCA* mutation carriers [16].

Conversely, MRI ? mammogram was the most costly intervention for both BRCA1 and BRCA2 mutations carriers, but had the highest QALYs from a societal perspective (Table 4) for both *BRCA1* and *BRCA2* carriers. In sensitivity analysis, if the cost of MRI was reduced by 75% to $305, then annual imaging was cost effective compared to mammogram alone. Similarly, Moore et al. recently reported an ICER of less than $50,000 per QALY for MRI at a cost <$315, compared to mammogram alone among women followed for over 25 years [22]. Without this cost reduction, the ICER of MRI was $179,599 compared to mammography alone, similar to our estimates of a follow up over a a 35-year period.

In our simulated cohort, using the preferences of *BRCA1* and *BRCA2* mutation carriers (Table 4), the most favorable ICERs of this study were prophylactic oophorectomy for *BRCA1* at $1,677 per QALY and *BRCA2*, at $4,535 per QALY. Despite their high preference ratings, the imaging modalities were dominated by preventive surgeries because MRI and mammography are recurring, expensive annual events, which add up to the expense of diagnosis and treatment [20] compared to prevention. Both modalities, especially MRI, result in many false positives, which can lead to psychological stress and unnecessary biopsies [3]. Over time, however, the readings may become more accurate and effective in differentiating benign tissue from cancer [2, 3].

The analyses performed previously by us have shown that outcomes vary depending on the ages of those being tested for *BRCA1/2*, the penetrance and prevalence of the mutations, the efficacy of preventive strategies, the preference ratings applied to those strategies, the morbidity and mortality of the disease itself, and the accuracy of screening (positive and negative predictive value) [2, 17].

In a previous model of ours, age remained an important predictor of comparative effectiveness from a health policy perspective. Many women are reluctant to have prophylactic oophorectomy before age 35 or until they have had a family. However, the previous research performed by us indicates that the cost effectiveness of testing rises, and therefore worsens, rapidly as the age at screening and prevention increases [19]. Women can postpone decisions regarding oophorectomy using oral contraceptives for a number of years

and postpone mastectomy using MRI to identify early-stage cancers [47, 48]. The analysis in this study indicates that in a high-risk population, screening with MRI is effective (Table 4), although expensive. Many women with *BRCA2* mutations attending high-risk clinics are offered tamoxifen, which, especially if used after oophorectomy, may reduce breast cancer risk [10], but some women and physicians are reluctant to use tamoxifen because of its potential side effects and the lack of evidence that it benefits mutation carriers specifically [49]. Trials of chemopreventive strategies including tamoxifen, raloxifene, and aromatase inhibitors are needed among populations at increased risk, such as Ashkenazi Jewish women with family histories of cancer.

A possible limitation of this study is the lack of data supporting our assumptions about stage distribution, given the screening by MRI and mammography versus mammography alone. We assumed that the stage distribution of breast cancer among women who received MRI would be the same as that of the cases in a cohort who received yearly MRI and mammography [2, 3, 14] and that the stage distribution among women who had mammography alone would be the same as that among high-risk women in the control arm of the NSABP BCPT tamoxifen trial [33], who had yearly mammograms. These assumptions may be biased because the women in both groups were trial participants and may, therefore, have had more careful surveillance than might be expected outside a research setting, but in our model, the difference had little effect on survival.

Both payers and policy makers should be aware of the potential benefits of MRI imaging and make efforts to bring the costs of screening down for all the high-risk women who wish to forego preventive surgery, at least for a set amount of time. In Canada, MRI costs 20% less than in the United States, and in England the cost may be even lower. Many women may wish to combine MRI with prophylactic oophorectomy, as we have done in our modeling. It may also be possible to conduct randomized trials to test the effects of tamoxifen, raloxifene, and aromatase inhibitors, with and without prophylactic oophorectomy.

The strategies that we analyzed varied little in overall effectiveness (Appendix: Figures 2 and 3). The differences in cost effectiveness were driven by differences in cost, especially the high cost of annual MRI. In our models, MRI was the most effective strategy because of its high preference rating and because its high sensitivity was associated with long survival. However, it was by far the most expensive of the strategies because it involves a costly and recurrent procedure and because it leads to many negative biopsies and possible overdiagnosis. Weinstein and Skinner [50] recently described the complexity of controlling costs given such constraints as geography, the structure of health care, and the value of particular treatments to the patient.

For known mutation carriers, preventive options are now a reality. Given that randomized trials comparing those options are unlikely to be conducted in the foreseeable future, we hope that our model results will provide policy makers and health care providers with some interim guidance. However, we should at least conduct observational studies to track utilization and to improve assessment of the available preventive options.

Average-risk women, especially those who are premenopausal, also need better preventive measures. We now know that breast and ovarian cancer can be prevented. We need to build on this knowledge to develop more evidencebased, acceptable, and affordable strategies to improve cancer outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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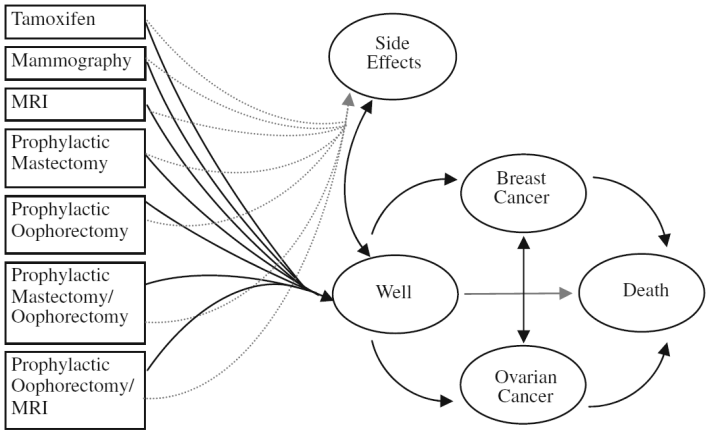

Fig. 1.
Markov model of *BRCA1/2* health states

Table 1

Incidence, preventive strategy risk reduction, and mortality assumptions used in the Markov model

Variable	Value
Health states per 100 persons per year ± SE, n	
Breast cancer [19, 28]	
BRCA 1 mutation carrier	3.32 ± 0.63
BRCA 2 mutation carrier	3.79 ± 1.07
BRCA 1 and *BRCA 2*	3.43 ± 0.556
Ovarian cancer [19, 28]	
BRCA 1 mutation carrier	1.55 ± 0.304
BRCA 2 mutation carrier	0.523 ± 0.031
BRCA 1 and *BRCA 2*	1.12 ± 0.285
Endometrial cancer due to tamoxifen [33]	0.401 ± 0.019
Pulmonary embolism due to tamoxifen [33]	0.320 ± 0.180
Cataracts due to tamoxifen [33]	0.110 ± 0.050
Preventive strategies ± SE, %	
Breast cancer risk reduction due to	
Prophylactic bilateral mastectomy [19, 51]	90 ± 5
Mastectomy and oophorectomy [9, 51]	95 ± 5
Tamoxifen [19, 33]	49 ± 7
Oophorectomy before age 50 years [8, 9, 37, 52]	47 ± 1
Ovarian cancer risk reduction due to	
Oophorectomy BRCA1 [6, 8, 36, 37]	96 ± 3
Oophorectomy BRCA2 [6, 8, 36]	96 ± 3 *
Oral contraceptives [47]	54 ± 11
Estrogen receptor+ by age and mutation % [35]	
BRCA1	
30–49	18% ± 2
50–69	22% ± 2
≥70	24% ± 2
BRCA2	
30–49	62% ± 2
50–69	75% ± 2
≥70	83% ± 2
Mortality	
Breast cancer	1 – SEER survival rates ≤0–16 years after diagnosis; U.S. population mortality rates thereafter [29]
Ovarian cancer	1 – SEER survival rates ≤0–10 years after diagnosis; U.S. population mortality rates thereafter [29]
Endometrial cancer	1 – SEER survival rates ≤5 years after diagnosis; U.S. population rates >5 years, includes 15% of mixed Mullarian tumors 0–5 years after diagnosis [31]; U.S. population rates [29, 33]
Pulmonary embolism	3% in first year; U.S. population rates after 1 year

Variable	Value
	[29, 33]
Cataracts	U.S. population rates [29, 33]

*No ovarian cancer in one study of *BRCA2*+ women, but not statistically significant. Assumed 96 ± 0.03 [8]

Table 2

Medical costs used in the Markov model in terms of 2009 dollars[a,b]

Variable (reference)	Total costs (direct + indirect), US$
First year after diagnosis [53–59]	22,375[b] (DCIS) 74,149[b] (breast cancer) 107,619[b] (ovarian cancer)
Subsequent yearly costs [54, 56, 58–60]	6,506[c] (breast cancer) 11,831[b] (ovarian cancer)
Terminal care costs, last year of life [54, 58–61]	54,991 (breast cancer) 75,188 (ovarian cancer)
Surveillance (per NCCN guidelines) [61]	4,476 (without breast or ovarian cancer)
Terminal care costs, last year of life [59, 60, 62]	36,199 (without breast or ovarian cancer)
Other medical costs[b]	
Endometrial cancer[b] [19]	6,211
Pulmonary emboli[b] [19, 39]	5,173
Cataract surgery[b] [19]	3,987
Genetic testing and counseling [63]	3,175
Preventive strategies	
Tamoxifen cost per year for premenopausal women (for 5 years) [39]	727
Letrozole cost per year for postmenopausal women (for 5 years) [39, 64]	3,516
Prophylactic mastectomy [5, 6]	10,591
Prophylactic salpingo-oophorectomy [5, 6]	6,373
Both prophylactic mastectomy and salpingo-oophorectomy	16,964
Prophylactic salpingo-oophorectomy and tamoxifen <age 50 (includes cost per year for 5 years of tamoxifen) [39]	10,008
Screening strategies including work and 2009 dollars [20, 27, 54, 65]	
Bilateral screening mammogram	
Initial screening mammogram	129
Follow-up mammogram	120
Ultrasound	112
Mammographic-guided surgical biopsy	1,667
Ultrasound-guided core needle biopsy	716
Stereotactic biopsy	997
Ultrasound-guided fine needle biopsy	581
Average total diagnostic cost following mammographic screening	31
Bilateral screening MRI	
Initial screening MRI	1,219
Short interval follow-up MRI	940
MRI-guided surgical biopsy	2,131
MRI-guided core needle biopsy	1,199
Average total diagnostic cost following initial MRI	373

Variable (reference)	Total costs (direct + indirect), US$
Average total diagnostic cost following subsequent MRI	209

[a] The discount rate (range) was 3% (0–5%). *DRG* diagnosis-related group, *NCCN* National Comprehensive Cancer Network, *V/Q* ventilation-perfusion

[b] Adjusted by the Medical Consumer Price Index into 2009 US$ [65]

[c] Yearly costs for patients with breast cancer apply to years 2–16 after diagnosis. Cost for years >16 are the same as those for healthy women

Table 3

Preference ratings used for quality adjustment

Health states (reference)	Mean (SD) Controls	Preference ratings Mutation carriers
Perfect health[a]	1.00	1.00
Cancer states among high-risk women[a]		
Breast cancer	0.84 (0.18)	0.87 (0.20)
Ovarian cancer	0.83 (0.17)	0.84 (0.23)
Preventive measures[a]		
Tamoxifen	0.90 (0.16)	0.95 (0.14)
Prophylactic mastectomy	0.88 (0.17)	0.88 (0.22)
Prophylactic bilateral salpingo-oophorectomy	0.90 (0.14)	0.95 (0.10)
Both prophylactic surgeries	0.79 (0.21)	0.84 (0.23)
Mammogram	0.97 (0.11)	1.00 (0.004)
MRI	0.96 (0.13)	1.00 (0.005)
MRI and BSO	0.86 (0.18)	0.95 (0.01)
Other health states associated with tamoxifen[b]		
Endometrial cancer [19]	0.68	0.68
Pulmonary Emboli [19]	0.50	0.50
Cataract surgery [19]	0.68	0.68
Well with positive BRCA1 or BRCA2 test result[a] [40]	0.87 (0.16)	0.92 (0.15)
Death	0.00	0.00

[a]Preferences are based on responses to a time-trade-off questionnaire using a 0–1.00-point scale [40]

[b]Preferences are based on the literature and the time spent in that health state: 5 years for endometrial cancer, and 1 year each for pulmonary emboli and cataract surgery [19]

Table 4

Estimated cost effectiveness of screening and primary preventive interventions for *BRCA1* and *BRCA2* mutation carriers

Intervention	Mean (SD) cost in per subject	Incremental cost	Mean (SD) QALYs	Incremental QALYs	Incremental cost/ incremental QALYs
With quality-adjusted survival in life years (QALYs) based on preference ratings of women without known high risk					
BRCA1					
Both prophylactic surgeries	$150,986 ($3,152)	–	16.66 (2.80)	–	–
Prophylactic oophorectomy	$153,396 ($2,945)	$2,410	18.04 (1.43)	1.38	$1,741
Prophylactic mastectomy	$167,607 ($3,709)	$14,211	17.52 (1.65)	−0.52	Dominated
Prophylactic oophorectomy and MRI	$170,893 ($3,393)	$17,497	17.63 (1.90)	−0.41	Dominated
Tamoxifen	$172,353 ($3,887)	$18,957	17.43 (1.38)	−0.61	Dominated
Mammography	$179,639 ($4,098)	$26,243	18.08 (0.96)	−0.40	$681,333
Mammography and MRI	$192,429 ($4,169)	$12,790	18.08 (1.01)	−0.01	Dominated
BRCA2					
Both prophylactic surgeries	$140,684 ($3,387)	–	16.82 (1.60)	–	–
Prophylactic mastectomy	$146,505 ($3,378)	$5,821	17.97 (2.89)	1.15	Extended dominance[a]
Prophylactic oophorectomy	$147,106 ($3,586)	$6,422	18.22 (1.79)	1.40	$4,587
Tamoxifen	$154,725 ($3,197)	$7,618	17.81 (1.47)	−0.41	Dominated
Prophylactic oophorectomy and MRI	$164,039 ($3,465)	$16,932	17.84 (1.97)	−0.39	Dominated
Mammography	$165,843 ($4,123)	$18,736	18.44 (1.07)	0.21	$88,104
Mammography and MRI	$177,918 ($4,163)	$12,075	18.49 (1.13)	0.49	$247,645
With quality-adjusted survival in life years (QALYs) based on preference ratings of BRCA1/2 mutation carriers					
BRCA1					
Both prophylactic surgeries	$151,048 ($3,152)	–	17.49 (2.83)	–	–
Prophylactic oophorectomy	$153,395 ($2,945)	$2,347	18.89 (2.83)	1.40	$1,677
Prophylactic mastectomy	$167,559 ($3,709)	$14,163	17.64 (1.65)	−1.25	Dominated
Prophylactic oophorectomy and MRI	$170,899 ($3,393)	$17,504	18.92 (1.90)	0.02	$736,788
Tamoxifen	$172,321 ($3,887)	$1,422	18.22 (1,38)	−0.70	Dominated
Mammography	$179,617 ($4,098)	$8,718	18.55 (0.96)	−0.37	Dominated
Mammography and MRI	$192,418 ($4,169)	$21,519	18.66 (1.01)	−0.26	Dominated
BRCA2					
Both prophylactic surgeries	$140,674 ($3,387)	–	17.68 (1.60)	–	–
Prophylactic mastectomy	$146,440 ($3,378)	$5,766	18.10 (2.89)	0.41	Extended dominance[a]
Prophylactic oophorectomy	$147,069 ($3,586)	$6,395	19.09 (1.79)	1.41	$4,535
Tamoxifen	$154,681 ($3,197)	$7,612	18.70 (1.47)	−0.43	Dominated
Prophylactic oophorectomy and MRI	$164,045 ($3,465)	$16,976	19.16 (1.97)	0.072	$236,867
Mammography	$165,760 ($4,123)	$1,714	18.94 (1.07)	−0.23	Dominated
Mammography and MRI	$177,934 ($4,163)	$13,888	19.12 (1.13)	−0.05	Dominated
With survival in life years (LYs) only (no quality adjustment)					
BRCA1					
Both prophylactic surgeries	$151,023 ($2,959)	–	20.65 (0.53)	–	–

Intervention	Mean (SD) cost in per subject	Incremental cost	Mean (SD) QALYs	Incremental QALYs	Incremental cost/ incremental QALYs
Prophylactic oophorectomy	$153,387 ($3,145)	$2,365	20.38 (0.51)	−0.27	Dominated
Prophylactic mastectomy	$167,553 ($3,730)	$16,531	20.11 (0.50)	−0.54	Dominated
Prophylactic oophorectomy and MRI	$170,881 ($3,380)	$19,859	20.48 (0.51)	−0.17	Dominated
Tamoxifen	$172,327 ($3,886)	$21,304	19.86 (0.48)	−0.79	Dominated
Mammography	$179,628 ($4,065)	$28,605	19.70 (0.47)	−0.95	Dominated
Mammography and MRI	$192,402 ($4,184)	$41,380	19.83 (0.48)	−0.82	Dominated
BRCA2					
Both prophylactic surgeries	$140,688 ($3,394)	–	20.87 (0.52)	–	–
Prophylactic mastectomy	$146,528 ($3,882)	$5,840	20.57 (0.53)	−0.30	Dominated
Prophylactic oophorectomy	$147,082 ($3,810)	$6,394	20.56 (0.52)	−0.31	Dominated
Tamoxifen	$154,738 ($3,979)	$14,049	20.24 (0.50)	−0.63	Dominated
Prophylactic oophorectomy and MRI	$163,997 ($3,461)	$23,309	20.70 (0.50)	−0.17	Dominated
Mammography	$165,803 ($4,175)	$25,115	20.03 (0.49)	−0.84	Dominated
MRI and mammography	$177,929 ($5,004)	$37,240	20.23 (0.50)	−0.64	Dominated

[a]Reference [66]