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Cost Effectiveness of Risk-Reducing Mastectomy versus Surveillance in BRCA Mutation Carriers with a History of Ovarian Cancer

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Abstract

Background—The appropriate management of breast cancer risk in BRCA mutation carriers following ovarian cancer diagnosis remains unclear. We sought to determine the survival benefit and cost effectiveness of risk-reducing mastectomy (RRM) among women with BRCA1/2 mutations following stage II–IV ovarian cancer.

Design—We constructed a decision model from a third-party payer perspective to compare annual screening with magnetic resonance imaging (MRI) and mammography to annual screening followed by RRM with reconstruction following ovarian cancer diagnosis. Survival, overall costs, and cost effectiveness were determined by decade at diagnosis using 2015 US dollars. All inputs were obtained from the literature and public databases. Monte Carlo probabilistic sensitivity analysis was performed with a \$100,000 willingness-to-pay threshold.

Results—The incremental cost-effectiveness ratio (ICER) per year of life saved (YLS) for RRM increased with age and BRCA2 mutation status, with greater survival benefit demonstrated in younger patients with BRCA1 mutations. RRM delayed 5 years in 40-year-old BRCA1 mutation carriers was associated with 5 months of life gained (ICER \$72,739/YLS), and in 60-year-old

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BRCA2 mutation carriers was associated with 0.8 months of life gained (ICER \$334,906/YLS). In all scenarios, \$/YLS and mastectomies per breast cancer prevented were lowest with RRM performed 5–10 years after ovarian cancer diagnosis.

Conclusion—For most BRCA1/2 mutation carriers following ovarian cancer diagnosis, RRM performed within 5 years is not cost effective when compared with breast cancer screening. Imaging surveillance should be advocated during the first several years after ovarian cancer diagnosis, after which point the benefits of RRM can be considered based on patient age and BRCA mutation status.

BRCA1/2 mutation carriers face a higher lifetime risk of breast and ovarian cancer, ranging from 35 to 88% for breast cancer and 10 to 65% for ovarian cancer.^{1–4} Risk-reducing mastectomy (RRM) and salpingo-oophorectomy (RRSO) are effective strategies to significantly reduce the risk of cancer development.^{5–10} Current guidelines recommend that in unaffected mutation carriers, RRM be considered and that RRSO occur between the ages of 35 and 40 years and after completion of childbearing.⁹

Some women learn of their BRCA mutation status following receipt of a cancer diagnosis, and an estimated 10–20% of women with ovarian cancer harbor a BRCA1/2 mutation irrespective of family history.¹¹ Updated guidelines from the Society of Gynecologic Oncology (SGO) and National Comprehensive Cancer Network (NCCN) recommend consideration of genetic testing for all women with newly diagnosed high-grade epithelial ovarian cancer (EOC).^{12,13} The overall 5-year survival of ovarian cancer is 45.6%;¹⁴ however, BRCA1/2-associated ovarian cancer is associated with improved progression-free survival (PFS) and overall survival (OS).^{15–18} This unique subset of women may be left weighing the risk of future breast cancer against the competing risk of ovarian cancer mortality. The purpose of our study was to determine the survival benefit and cost effectiveness of RRM compared with surveillance in women with stage II–IV ovarian cancer who are subsequently found to be BRCA1/2 mutation carriers.

METHODS

This study was reviewed by the Duke University Institutional Review Board and was found to be exempt. A decision model was constructed from a third-party payer perspective using a modified Markov structure to compare the survival and costs associated with breast cancer risk reduction strategies for women with a new diagnosis of stage II–IV ovarian cancer and BRCA1/2 germline mutation: (1) screening with annual magnetic resonance imaging (MRI) and mammography; or (2) RRM performed 1–15 years after ovarian cancer diagnosis, assuming no disease recurrence/progression. The model was populated with the following exhaustive and mutually exclusive Markov states: alive without ovarian cancer recurrence; alive with ovarian cancer recurrence; alive with breast cancer and no ovarian cancer recurrence; alive with breast cancer and ovarian cancer recurrence; dead of ovarian cancer; dead of breast cancer; dead of other causes; long-term ovarian cancer survivor with no history of breast cancer; long-term ovarian cancer survivor who is alive with breast cancer <15 years prior; long-term breast cancer survivor who is alive with ovarian cancer recurrence <15 years prior; and long-term survivor of both breast and ovarian cancer. Women were followed from the age of ovarian cancer diagnosis to 100 years of age or death.

Age at ovarian cancer diagnosis was categorized into decades, with cut-points at 40, 50, 60 and 70 years of age. The model was run separately for BRCA1 versus BRCA2 carriers to account for the prevalence and individual effects of each mutation on breast and ovarian cancer mortality. Primary outcomes of the model included the mean cost, mean OS time, and cost effectiveness of each strategy. Costs were updated to 2015 US dollars; cost and effectiveness were discounted at 3% annually in the base cases, based on standards set by the Second Panel on Cost- Effectiveness in Health and Medicine.¹⁹ This accepted rate accounts for the loss in value when there is a delay in realizing the value of a health service. To provide the survival benefit of each strategy, differences in survival time between strategies were reported with and without discounting. Cost-effectiveness outcomes were only reported using discounting of both costs and life-years. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in cost by the difference in value. ICERs were reported per year of life saved (YLS). The threshold of \$100,000 is the most widely held value for determining cost effectiveness, although estimates of \$150,000 and \$200,000 are acceptable.²⁰ Several key assumptions were made, as described in Table 1.

Clinical Estimates

Breast cancer incidence and survival were obtained from primary sources or from the literature, as described below, and modeled as distributions based on the available data. Survival data were modeled as beta distributions, as previously described,²¹ while hazard ratios were modeled using normal distributions with incorporation of their reported confidence intervals (Table 2).

Breast Cancer Incidence—All patients in the study were assumed to have a new diagnosis of ovarian cancer. The incidence of breast cancer among mutation carriers was modeled as a beta distribution from a prospective study of 570 mutation carriers who underwent prophylactic mastectomy or active surveillance.²²

Cancer Survival—Survival outcomes were modeled annually as beta distributions using clinical data from the sources below.²³ Ovarian cancer PFS was modeled from an observational study of 316 BRCA1/2 mutation carriers with high-grade serous ovarian cancer (years 1–4), and from long-term (5–10 years) randomized trial data comparing platinum-based regimens for the primary treatment of EOC.^{24,25} PFS was adjusted using hazard ratios from a meta-analysis evaluating the impact of BRCA mutation type on survival,²⁶ and OS for the first 5 years after disease-progression was modeled from the OCEANS trial of platinum-sensitive recurrent ovarian cancer.²⁷ Age-specific survival from years 6–15 was modeled using Surveillance, Epidemiology and End Results (SEER) 18 registries, 1973–2012, and data were accessed via SEER*Stat v 8.2.1 (Surveillance Research Program, National Cancer Institute [NCI]). Cancer-specific survival was modeled for stage II–IV ovarian cancer together.

Breast cancer disease-specific survival was derived from the SEER 18 registries, 1973-2012, and data were accessed via SEER*Stat v 8.2.1 (Surveillance Research Program, NCI). Breast-cancer specific survival for BRCA2-associated cancers was assumed to mirror that of the general population.²⁸ Cancer-specific survival was obtained for stages II–IV, stratified

into ages 40–49, 50–59, 60–69, 70–79, and 80+ years. Among BRCA1 mutation carriers, we assumed that 80% would be estrogen receptor/progesterone receptor/HER2-negative (triple-negative breast cancer) and 20% would be non-triple-negative breast cancer.^{28,29} Modeled breast cancer-specific survival was based on long-term follow-up from a retrospective cohort analysis by Dent et al.³⁰

Death from Other Causes—Death from competing causes was modeled annually using US life tables.³¹

Costs

All costs were derived from published estimates as below, and costs were inflated to 2015 US dollars, as outlined in Table 2.³²

Breast Cancer Screening—The costs of mammographic screening and annual MRI for BRCA1/2 mutation carriers were derived from previously reported estimates and included average total diagnostic costs.^{12,33}

Risk-Reducing Mastectomy (RRM) and Breast Reconstruction—The costs of RRM for BRCA1/2 carriers were derived from previously published patient-level data.³⁴ We assumed that 82% of women undergoing RRM would undergo either immediate or delayed reconstruction.³⁵ Using previously published frequencies and costs, we calculated an average cost for RRM that accounted for the proportion of RRM patients who underwent reconstruction^{35,36} (Table 2).

Breast and Ovarian Cancer Treatment—Breast and ovarian cancer treatment costs were derived from the publication by Yabroff et al.³⁷

Sensitivity Analyses

Age at ovarian cancer diagnosis, BRCA mutation status, and the time to RRM following ovarian cancer diagnosis varied in the model. Furthermore, we modeled an alternative scenario in which the baseline risk of developing breast cancer was reduced by 50% following oophorectomy, chemotherapy, and omission of screening after ovarian cancer.

Monte Carlo probabilistic sensitivity analysis was performed to construct cost-effectiveness acceptability curves. In each simulation, 1000 first-order trials were performed in which each modeled parameter was sampled 1000 times from its distribution.

RESULTS

BRCA1 Mutation Carriers

Base-Case Analysis—Based on the expectation that women would not undergo RRM immediately following diagnosis and treatment for ovarian cancer, we defined the base case as RRM performed 5 years after an ovarian cancer diagnosis at age 50 years, if no ovarian cancer recurrence.

A BRCA1 mutation carrier diagnosed with ovarian cancer at age 50 years had an undiscounted life expectancy of 14.03 years (95% confidence interval [CI] 13.1–15.0) with MRI/mammogram screening, and 14.28 years (95% CI 13.3–15.2) with RRM at 5 years, a mean survival benefit of 3 months. The risk of dying of breast cancer was 6.1% with screening and 4.5% with RRM, while the risk of dying of ovarian cancer was 70% in both groups.

Using discounting of costs and effectiveness, the mean cost of the screening strategy in the base case was \$165,131 (95% CI \$163,816–\$166,518), compared with RRM at \$177,049 (95% CI \$175,420–\$178,719). The mean discounted life expectancy was 10.56 years (95% CI 10.0–11.1) for screening and 10.67 years (95% CI 10.1–11.2) for RRM. RRM had an ICER of \$109,615/YLS compared with screening. In acceptability curve analysis, RRM delayed 5 years was cost effective in 38% of simulations at a willingness-to-pay of \$100,000/YLS (see Table 3).

BRCA2 Mutation Carriers

Base-Case Analysis—A BRCA2 carrier diagnosed with ovarian cancer at age 50 years had an undiscounted life expectancy of 16.83 years (95% CI 15.4–18.3) with MRI/mammogram screening, and 16.99 years (95% CI 15.5–18.5) with RRM delayed 5 years, a mean gain of 1.9 months. The risk of death from breast cancer was 2.9% with screening and 1.8% with RRM, while the risk of death due to ovarian cancer was 61.9% for both groups.

Using discounting of costs and effectiveness, the mean cost of the screening strategy in the base case was \$163,990 (95% CI \$162,293–\$165,592), compared with RRM at \$175,536 (95% CI \$173,517–\$177,395). The mean discounted life expectancy was 12.13 years (95% CI 11.4–13.0) for screening and 12.2 years (95% CI 11.5–13.1) for delayed RRM. RRM had an ICER of \$168,482/YLS compared with screening. In acceptability curve analysis, RRM delayed 5 years was cost effective in 13% of simulations at a willingness-to-pay threshold of \$100,000/YLS (Table 3).

Sensitivity Analyses for Time to RRM

Cost Per Year of Life Saved (YLS)—In BRCA1 carriers diagnosed with ovarian cancer at age 50 years, delayed RRM exceeded the common willingness-to-pay threshold of \$100,000/YLS until year 4. After year 5, the ICER for mastectomy fell below \$100,000/YLS and RRM became cost effective. These trends were similar, but with somewhat higher ICERs, for BRCA2 carriers. The effect of time to mastectomy (TTM) on cost per YLS is depicted in Fig. 1a, b.

Mastectomies Per Breast Cancer Prevented—When ICER was modeled as mastectomies per breast cancer prevented, RRM 1 year following ovarian cancer diagnosis at age 50 years was associated with 10 and 6.5 mastectomies per breast cancer prevented in BRCA1 and BRCA2 mutation carriers, respectively. At 4 years after ovarian cancer diagnosis, the ICER then fell to two to three mastectomies per breast cancer prevented for both groups (Fig. 2).

Sensitivity Analyses for Age of Ovarian Cancer Diagnosis

Cost per YLS—For BRCA1 mutation carriers diagnosed at age 40 years, RRM performed 5 years after ovarian cancer diagnosis was associated with a 5-months survival gain and an ICER of \$72,739/YLS. For BRCA1 carriers diagnosed at age 70 years, RRM performed 5 years after ovarian cancer diagnosis was associated with a less than 1-month survival gain, with an ICER of \$485,730/YLS. Similarly, for BRCA2 mutation carriers diagnosed at age 40 years, RRM performed at 5 years was associated with a 3.6-month survival gain and an ICER of \$103,562/YLS. The effect of age at ovarian cancer diagnosis on cost per YLS is further depicted in Table 3 and Fig. 1.

Alternative Scenarios

Lower Breast Cancer Incidence in the Absence of Screening—An alternative scenario assumed that breast cancer incidence was reduced by 50% when screening was discontinued following a diagnosis of ovarian cancer. In this scenario, RRM delayed by 5 years in a BRCA1 mutation carrier diagnosed at age 50 years became slightly less cost effective, with the ICER rising to \$114,012/YLS.

Lower Baseline Probability of Breast Cancer—An alternative scenario assumed that breast cancer risk was reduced by 50% following prior treatment for ovarian cancer, regardless of screening status. This has been previously demonstrated as an hypothesized result of primary treatment with either RRSO or chemotherapy [38]. For a 50-year-old woman with a BRCA1 mutation and ovarian cancer, this resulted in a reduced lifetime risk of breast cancer from 24 to 14%. Similarly, the baseline probability of dying from breast cancer dropped from 6 to 3.7%. In this scenario, RRM at 5 years after ovarian cancer diagnosis resulted in an ICER of \$192,959/YLS compared with breast screening.

DISCUSSION

Our study compares the survival benefit and cost effectiveness of breast cancer risk-reduction strategies in BRCA1/2 mutation carriers affected by ovarian cancer, and demonstrates that the survival benefit and cost effectiveness of these strategies depend on age at ovarian cancer diagnosis and on TTM. RRM was not cost effective in the first 3–4 years after ovarian cancer diagnosis in any scenario. For BRCA1/2 mutation carriers aged 40–50 years, RRM performed 5 years after ovarian cancer diagnosis was associated with a survival benefit of 2–5 months and was considered cost effective, with a generous ICER of < \$200,000/YLS. RRM was most cost effective among the youngest BRCA1 cohort from 40 to 50 years of age, the only group meeting the conservative ICER threshold of < \$100,000. Among women diagnosed with ovarian cancer at age 60 years or later, the survival benefit of RRM was negligible and the ICER exceeded the willingness-to-pay threshold of \$200,000/YLS in three of four scenarios. Furthermore, we found that the ratio of prophylactic mastectomies per breast cancer prevented was highest in the first few years after ovarian cancer diagnosis.

Several retrospective studies have reported a low risk of breast cancer in BRCA mutation carriers following ovarian cancer diagnosis and treatment. Gangi et al. reported the

development of breast cancer in 8.9% (12/135) of BRCA1/2 mutation carriers with a history of ovarian cancer, with mean time to breast cancer diagnosis of 50.5 months [39]. Additionally, the majority of breast cancers were detected mammographically, questioning the value of MRI surveillance in this subset of women. Vencken et al.³⁸ demonstrated a 6% 5-year risk of primary breast cancer in 79 women with BRCA-related ovarian cancer, compared with a 16% 5-year risk in unaffected BRCA mutation carriers. Domchek et al.⁴⁰ reported excellent breast cancer-free survival in a cohort of 164 women with BRCA-related ovarian cancer. At 5 and 10 years after ovarian cancer diagnosis, breast cancer-free survival was 97 and 91%, respectively, and all deaths in this cohort were due to ovarian cancer.⁴⁰ These data, as well as our own, support the use of less aggressive breast cancer risk-reduction strategies in the first several years after ovarian cancer diagnosis and treatment.^{39,40}

For select patients with prolonged disease-free survival following treatment for ovarian cancer, RRM may be warranted. The survival benefit of up to 5 months may be meaningful in women with advanced ovarian cancer, even with the accompanying surgical morbidity of RRM. In a recent survey-based study of patients with ovarian and other gynecological malignancies, patients stated a preference to undergo chemotherapy with greater toxicity if it afforded them at least a 5- to 6-month gain in OS, or 3–4 months of PFS without toxicity.⁴¹ For some BRCA mutation carriers, the benefits of RRM may outweigh the risks, even after ovarian cancer.

There are several limitations to our study. Our model was limited by its reliance on previously published data from different years in different populations. Estimates of cost were based on several different studies, and estimates of procedure-specific breast reconstruction costs and frequencies were limited to studies of women with prior breast cancers. These studies were chosen due to their inclusion of hospital costs, specifically the overall costs of the most frequently completed breast reconstruction techniques, and included the costs of complications. These estimates were derived from the both the Medicaid fee schedule and the Nationwide Inpatient Sample, and were adjusted for inflation. In addition, we did not include other preventive strategies, including chemoprevention. Additionally, we were unable to incorporate changes in quality of life for each strategy, based on a paucity of data addressing this issue.

CONCLUSIONS

Our findings suggest that RRM in the first several years after an ovarian cancer diagnosis is unlikely to be associated with substantial survival gain or to be cost effective for many BRCA mutation carriers with a history of ovarian cancer. The gains in life expectancy should be weighed against the surgical morbidity and anticipated quality of life after mastectomy in a population faced with decreased projected survival. Ultimately, we hope that our findings contribute to the management of breast cancer risk in this unique and increasing population of women with a history of ovarian cancer and known BRCA1/2 mutation.

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FIG. 1. Incremental cost-effectiveness ratio (ICER) for risk-reducing mastectomy in **a** BRCA1 carriers and **b** BRCA2 carriers

FIG. 2.

Number of mastectomies per breast cancer prevented based on time to risk-reducing mastectomy following ovarian cancer diagnosis

TABLE 1

Key assumptions included in the model

1. Women with a <i>BRCA1/2</i> mutation are at increased annual risk of developing breast cancer. Annual risk depends on the choice between screening and risk-reducing mastectomy and is modeled based on a cohort study of mutation carriers with long-term follow-up ²²
2. Women with a <i>BRCA1/2</i> mutation and breast or ovarian cancer diagnosis have cancer-specific survival outcomes dependent on the specific <i>BRCA</i> mutation and type of cancer, as defined by a prior meta-analysis ²⁶
3. Women who remain alive following an ovarian cancer diagnosis remain at risk of developing breast cancer until death from ovarian cancer or death from other causes
4. Women are considered long-term <i>ovarian cancer survivors</i> if (1) they are without evidence of disease recurrence or progression 7 years after ovarian cancer diagnosis, or (2) they are alive 15 years after ovarian cancer recurrence. Long-term <i>ovarian cancer survivors</i> are considered to no longer be at risk of death from ovarian cancer
5. Women are considered long-term <i>breast cancer survivors</i> if they are alive without evidence of recurrence 15 years after breast cancer diagnosis. Long-term breast cancer survivors are considered to no longer be at risk of dying from breast cancer
6. Women receiving imaging surveillance receive both MRI and mammogram annually until ovarian cancer progression occurs or breast cancer is diagnosed

TABLE 2

Model inputs

Clinical estimates	BRCA1	BRCA2
Overall mortality for breast cancer ²⁶	1.5 (1.11–2.04) ^a	0.97 (0.69–1.30) ^a
Overall mortality for ovarian cancer ²⁶	0.76 (0.7–0.83) ^a	0.58 (0.50–0.66) ^a
Prevalence of BRCA1/2 among women with ovarian cancer ⁴²	0.11	0.06
Breast cancer-specific mortality after RRM ²²	0.29 (0.03–2.61) ^b	
Cost estimates	Mean cost (2015 US\$)	
Screening and surveillance imaging ¹²		
First year		2082
Annual		11,545
Annual treatment costs of breast cancer ³⁷		
Initial year		16,887
Annual		1728
Final year		42,046
Annual treatment costs of ovarian cancer ³⁷		
Initial year		74,229
Annual		5604
Final year		72,222
Surgical and hospital costs of RRM		
RRM without reconstruction ³⁴		16,123
RRM plus tissue expander ³⁶		44,294
RRM plus direct-to-implant ³⁶		41,026
RRM plus autologous/DIEP ³⁶		24,017
Calculated weighted average for cost of RRM		35,561

RRM risk-reducing mastectomy, DIEP deep inferior epigastric perforator

^a95% confidence interval-hazard ratios for breast and ovarian cancer mortality among BRCA1/2 mutation carriers compared with non-carriers

^b95% confidence interval-hazard ratios for breast cancer-specific mortality after RRM, with screening being the reference group

TABLE 3

Comparison of breast cancer risk-reduction strategies in BRCA mutation carriers based on age at ovarian cancer diagnosis

Strategy	Age at OC diagnosis (years)	Overall survival (years)		Survival gains ^a (months)		Lifetime risk of breast cancer death (%) ^b		ICER (\$/YLS)	
		BRCA1	BRCA2	BRCA1	BRCA2	BRCA1	BRCA2	BRCA1	BRCA2
Screening	40	16.20	19.97			7.1	3.6		
	50	14.03	16.83			6.1	2.9		
	60	11.89	13.78			4.9	2.2		
	70	9.71	10.80			3.4	1.5		
RRM	40	16.62	20.27	5.0	3.6	5.2	2.1	72,739	103,562
	50	14.28	16.99	3.0	1.9	4.5	1.8	109,615	168,482
	60	12.00	13.85	1.3	0.84	3.9	1.5	195,612	334,906
	70	9.75	10.83	0.5	0.36	2.9	1.1	485,730	914,077

OC ovarian cancer, RRM risk-reducing mastectomy, ICER incremental cost-effectiveness ratio, YLS year of life saved

^aSurvival gains with RRM compared with screening as the reference

^bLifetime risk of breast cancer death assuming no ovarian cancer recurrence