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Was Angelina Jolie Right? Optimizing Cancer Prevention Strategies Among BRCA Mutation Carriers

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Abstract. Female carriers of a BRCA1 or BRCA2 genetic mutation face significantly elevated risks of cancer, with 45%–65% of women developing breast cancer and 15%–39% developing ovarian cancer in their lifetimes. Prophylactic surgery options to reduce cancer risk include a bilateral mastectomy (BM), bilateral salpingo-oophorectomy (BSO), or both surgeries. No comprehensive model providing recommendations at which age to perform the surgeries to optimize quality-adjusted life years (QALYs) exists. Using available clinical data, we develop a Markov decision process model of a mutation carrier's health states and corresponding transitions, including age-dependent breast and ovarian cancer risk, distribution of each cancer subtype and stage, and mortality. We convert the problem to a linear program to solve for the optimal surgery sequence that maximizes the carrier's expected lifetime QALYs under varying assumptions about individual patient preferences on post-surgery quality of life, fertility considerations, advances in cancer screening or treatment, and others. Baseline results demonstrate that a QALY-maximizing sequence recommends BM between ages 30 and 60 and BSO after age 40. Surgeries are recommended later for BRCA2 mutation carriers, given their lower risk for both cancers compared to BRCA1 mutation carriers. We derive structural properties from the model and show that when a carrier has already undergone one surgery, there exists an optimal control limit beyond which performing the other surgery is always QALY maximizing.

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Keywords: healthcare • Markov decision process • decision analytic model • linear programming • breast cancer • ovarian cancer • BRCA mutation

1. Introduction

Every year, more than 1.7 million women worldwide are diagnosed with breast cancer, the most common cancer in women, accounting for 25% of all female malignancies (World Cancer Research Fund International 2015). Ovarian cancer, the seventh most common cancer in women, is diagnosed in 239,000 women annually (World Cancer Research Fund International 2015). Approximately 5%–10% of breast cancers are attributable to mutations in the BRCA1 or BRCA2 gene, whose typical role is to suppress tumor formation and growth (Breastcancer.org 2017). One in every 400 to 800 women carries a BRCA1 or BRCA2 genetic mutation, although the prevalence is greater in certain populations, including those of northern European descent, some Hispanic populations, and women of Ashkenazi Jewish descent—among whom 1 in 50 carries a BRCA1/2 mutation (Hall et al. 2009, John et al. 2007). More than 2,000 variants in BRCA1 and BRCA2 genes are known, and female mutation carriers face significantly elevated risks of both breast and ovarian cancer (Karami and Mehdipour 2013). An estimated 55%–65% (BRCA1) and 45% (BRCA2) of female carriers develop breast cancer in their lifetime, compared to 12% in the general population (Antoniou et al. 2003, Chen and Parmigiani 2007). The lifetime risk of ovarian cancer is

slightly lower at 39% (BRCA1) and 11%–17% (BRCA2), but far greater than the 1%–2% lifetime risk among the general population (Antoniou et al. 2003, Chen and Parmigiani 2007).

Women with a known BRCA mutation can improve early cancer detection by undergoing enhanced surveillance with frequent mammograms and magnetic resonance imaging (MRI) scans, and potentially reduce the risk of developing cancer with chemoprevention and/or prophylactic surgery. Surgically removing both breasts, known as a bilateral mastectomy (BM), can reduce a carrier's lifetime risk of breast cancer by as much as 95%; removing both ovaries and fallopian tubes, known as a bilateral salpingo-oophorectomy (BSO), can reduce ovarian cancer risk by 80% and additionally reduce breast cancer risk by up to 60% (Domchek et al. 2006, 2010; Eisen et al. 2005; Grann et al. 1999a; Rebbeck et al. 2009). Following actress Angelina Jolie's revelation in 2013 that she carries a BRCA1 mutation and candid discussion of her own decision to undergo a preventive BM (Jolie 2013) and BSO two years later (Jolie 2015), studies have reported an "Angelina Jolie effect," with referrals for genetic testing increasing twofold (Evans et al. 2014) and rates of preventive bilateral mastectomies also more than doubling (Evans et al. 2015).

As both surgeries are invasive procedures with possible complications, hormonal side effects, and fertility implications, deciding whether to undergo such procedures—and at what age—is a difficult choice for many women. The benefits of decreased cancer risk and peace of mind are often weighed against a reduction in quality of life (QOL). BRCA mutation carriers will increasingly face this trade-off, with more women learning of their own mutation status before a potential cancer diagnosis as less expensive genetic testing becomes widely available (Long and Ganz 2015).

While the risk-reducing benefits of a BM and BSO are widely accepted, no detailed guidelines currently exist to advise women at which age each surgery should be performed. The National Comprehensive Cancer Network (2016) advises physicians to discuss the option of BM with BRCA mutation carriers and suggests that a BSO be performed between ages 35 and 40 or after completion of child bearing. Yet these recommendations fail to differentiate between BRCA1 and BRCA2, do not specify a recommended age to undergo BM, and do not incorporate patient QOL considerations. Other publications offer comparisons of cancer prevention strategies (Schrag et al. 1997, Grann et al. 1999b), or provide information about cancer and mortality risk under different strategies (Kurian et al. 2014). However, a comprehensive model to optimize patient outcomes such as expected quality-adjusted life years (QALYs) or survival probability is still lacking.

In this study, we contribute to the existing literature by developing a comprehensive Markov decision process (MDP) model of a BRCA1 or BRCA2 mutation carrier's health states and the potential impact of her decisions to undergo prophylactic surgery on both breast and ovarian cancer risk, survival, and QOL. As the problem's state space is too large to solve directly with dynamic programming (DP), we transform the problem of optimizing health outcomes into a form solvable through linear programming (LP) and we identify a QALY-maximizing sequence of prophylactic surgeries. To account for the uncertainty about numerically estimated model parameters and carrier-specific preferences of surgeries' impact on QOL, we conduct various sensitivity and robustness analyses. We additionally exploit the model's structural properties to analytically derive monotone decision policies, which complement the numerical results. Our model could help healthcare professionals in improving their counseling of mutation carriers since patients can provide individualized QOL preferences for surgery.

Our baseline results find that it is optimal for BRCA1 mutation carriers to undergo BM starting at age 30 up until age 60, after which BM is no longer recommended, and to undergo BSO from age 40 onward to maximize cumulative QALYs. For BRCA2 mutation carriers, the window for recommended BM reduces to ages 40 to 46, after which this surgery is no longer QALY maximizing, and the optimal age to undergo BSO is delayed to age 49 or later, as the overall cancer risk is lower than for BRCA1 mutation carriers.

The remainder of this paper is organized as follows: Section 2 provides an overview of the existing literature on estimating cancer risk among BRCA1/2 mutation carriers and prophylactic surgery options to reduce risk, assessing quality of life, and the use of MDP models as decision aids in healthcare. The structure of our MDP model is briefly summarized in Section 3, with additional details provided in Appendix B,

and methods for solving it are given in Section 4. Numerical results of the optimization approach are presented in Section 5, and we conclude with discussion and policy implications in Section 6.

2. Literature Review

2.1. BRCA and Cancer Risk

The link between early onset of breast cancer and genetic mutations was first discovered in 1990 for BRCA1 (Hall et al. 1990) and 1994 for BRCA2 (Wooster et al. 1994). In their meta-analysis for female mutation carriers aged 20 to 70 years old, Chen and Parmigiani (2007) report mean cumulative breast cancer risks of 57% (BRCA1) and 40% (BRCA2), and ovarian cancer risks of 40% (BRCA1) and 18% (BRCA2). The annual risk of either cancer appears to generally increase with age, with a substantial increase after age 40.

Clinical studies provide evidence that breast cancer risk in BRCA mutation carriers is reduced by undergoing a prophylactic BM, BSO, or both procedures. A preventive BM reduces breast cancer risk by approximately 90%, as minimal breast tissue remains that could develop cancer (Rebbeck et al. 2004, McDonnell et al. 2001). Following a BSO, ovarian cancer risk is reduced by an estimated 80% because the organs themselves are removed (Rebbeck et al. 2009). A BSO procedure additionally lowers breast cancer risk by 30% to 60% depending on the age at surgery (with a greater reduction in cancer risk at earlier ages) due to reduced estrogen production, which can fuel growth in certain breast cancer subtypes (typically luminal A/B) (Eisen et al. 2005). Among carriers who undergo both BM and BSO procedures, breast cancer risk is reduced by 95% (Rebbeck et al. 2004).

Overall, the medical literature consistently demonstrates the benefits of a BM and BSO at reducing cancer incidence, thereby significantly prolonging life expectancy, often by several years, depending on the age of prophylactic surgery (Salhab et al. 2010). Domchek et al. (2006) find a positive effect of prophylactic BSO on overall survival as well as breast- and ovarian-cancer-specific mortality of mutation carriers. Their findings are in line with those of other clinical studies (Domchek et al. 2010, Kauff et al. 2008) and are confirmed by a meta-analysis of 10 published studies (Rebbeck et al. 2009).

2.2. Quality of Life

Despite clear evidence of survival gains following prophylactic surgery in BRCA mutation carriers, there is less agreement on each surgery's impact on QOL, defined as a patient's health-related utility given a specific condition or disease, and ranging in value between 1 (corresponding to perfect health) and 0 (death). For a prophylactic BM, Grann et al. (1999a, 2010) report a reduced long-term QOL based on empirical evidence collected from questionnaires administered to women with an increased risk of breast cancer and a control group. A temporary lower QOL is suggested by Barton et al. (2005), who find that two-thirds of women undergoing a BM suffer from at least one, mostly reversible, complication. Several other studies find no long-term effects of a BM on quality of life. The two study populations examined by Tercyak et al. (2007) consist of women with a BRCA1/2 mutation and unilateral breast cancer who chose a contralateral mastectomy (i.e., surgically removing the other noncancerous breast) or breast-conserving surgery (i.e., removing only the breast tumor and nearby tissue) as a treatment option. Their results did not show a significantly lower QOL associated with a BM. Geiger et al. (2006) draw similar conclusions after comparing QOL between women who were diagnosed with unilateral breast cancer and chose either a contralateral mastectomy or other treatment options.

Published studies examining QOL following a BSO also show heterogeneous estimates, with most studies reporting lower long-term quality of life (Grann et al. 1999a, 2010). A review by Shuster et al. (2008) suggests that reduced QOL after a BSO depends on the surgery's timing relative to the onset of natural menopause, because of the increased risk of negative side effects including osteoporosis, cardiovascular disease, and decline in sexual activity. Their review indicates a lower QOL among premenopausal women undergoing a BSO, as the surgery inhibits fertility and immediately leads to surgically induced menopause. Fry et al. (2001) do not find significant differences in QOL among women who undergo a prophylactic BSO versus those who choose a screening program instead, although women report lower health utilities on some subscales after a BSO. Similar conclusions are drawn by Madalinska et al. (2005), Michelsen et al. (2009), and Robson et al. (2003). For an extensive

review of the literature in this area, we refer readers to Harmsen et al. (2015).

2.3. Decision Analytic Models

Models using Markov decision processes have been applied to several topics in healthcare; an overview is summarized by Alagoz et al. (2010). Most applications relate to the optimal treatment of a particular disease, with breast cancer one of the prevailing diseases that is modeled. Several papers use MDPs to determine the optimal breast cancer screening frequency or treatment guidelines based on screening results. Ayer et al. (2012) use a partially observable MDP to determine personalized mammography schedules based on a woman's screening history and personal risk factors. Chhatwal et al. (2010) and Alagoz et al. (2013) both provide numerical results and structural properties of an MDP model to improve decisions regarding follow-up actions after a mammogram.

In the medical literature, some studies use simpler Markov models of transitions between health states of BRCA mutation carriers to examine different cancer prevention strategies and outcome measures. Kurian et al. (2012) provide a decision support tool that computes survival probabilities for both BRCA mutation types based on a woman's age at time of surgery. Schrag et al. (1997) use a Markov model with data from clinical studies to compare the resulting life expectancy of nine different prevention strategies, each varying either in the procedure(s) performed or their timing. One of their findings suggests that delaying a BSO for 10 years at the age of 30 has limited impact on life expectancy. Grann et al. (2002) and Schrag et al. (2000) consider tamoxifen therapy as an additional option, while Armstrong et al. (2004) assess the effect of hormone replacement therapy on outcomes following a BSO. In addition to measuring survival benefits, quality-adjusted outcome measures like QALYs are used by Grann et al. (1998) and van Roosmalen et al. (2002). Anderson et al. (2006) analyze the cost-effectiveness of different prevention strategies.

Simple Markov chain models are limited to static decision policies, whereas in real life, women will typically make repeated decisions regarding prophylactic surgery type and timing. In this context, determining an optimal policy requires a Markov decision process and an appropriate solution methodology, such as dynamic programming. Abdollahian and Das (2015) develop an MDP to compute the optimal timing of prophylactic BM and BSO to achieve a cost- or QALY-optimal strategy for mutation carriers. They find that for a BRCA1 mutation carrier, the QALY-optimal strategy would be a BSO at age 30 and a BM at age 50. Although their model optimizes a carrier's accumulated QALYs, it does not track changing health states after a cancer diagnosis, such as the subsequent development of the other (breast/ovarian) cancer type. Their model also simplifies the heterogeneity of cancer subtypes (i.e., luminal A/B, human epidermal growth factor 2 (HER2), triple negative (TN)), which impacts mortality (Parise and Caggiano 2014). This an important distinction, as BRCA-related breast cancers differ from non-BRCA-related cancers in their more aggressive nature (Mavaddat et al. 2012). Therefore, a model that is calibrated to overall breast cancer survival rates may misestimate a BRCA mutation carrier's life expectancy following a cancer diagnosis.

The existing literature offers limited guidance to female BRCA mutation carriers and their physicians regarding the optimal timing of prophylactic surgeries. Studies either lack the ability to choose an optimal strategy from all relevant decision alternatives, or require simplistic assumptions that ignore important characteristics of breast and ovarian cancer progression. We contribute to the literature in three ways. First, we develop a comprehensive decision analytic model for BRCA1/2 mutation carriers that is also computationally tractable and capable of finding the optimal surgery sequence. Second, we exploit the structural properties of a simplified model version and analytically derive monotone decision policies, which could help foster a better understanding of the model's results in certain circumstances. Third, we provide insights into the influence of a carrier's personal preferences regarding postsurgery quality of life, fertility considerations, and prior history of breast or ovarian cancer, as well as other variations in model parameters.

3. Model Formulation

We formulate a Markov decision process model of the prophylactic surgery decision faced by female BRCA1/2 mutation carriers: at what age(s) to undergo a BM and/or BSO to reduce breast and ovarian cancer risk to maximize quality-adjusted life expectancy. We

begin with a finite-horizon model with yearly decision epochs.

Carriers are assumed to be healthy initially with no prior history of breast or ovarian cancer, to have not previously undergone a BM or BSO surgery, and to be eligible for surgery starting at age 20, although we later relax these assumptions in sensitivity analyses. The model's states correspond to various health states, including diagnosis of breast cancer or ovarian cancer and associated tumor subtypes and stages. Undergoing a BM or BSO reduces the risk of breast cancer only or both breast and ovarian cancer, respectively. A carrier's mortality rate and QOL depend on her age and health state. Should a cancer diagnosis occur, a cancer-specific mortality rate that depends on the tumor site (breast or ovaries), stage, and subtype (for breast cancer only) is added to the baseline mortality rate. Model parameters differ between the two mutation types wherever evidence from clinical studies could be found.

3.1. State Space

The state space $S = \{age, surg, bc, bcts, bcsu, oc, octs, de\}$ consists of eight variables, which each take on a value from a finite set, described below (Table A.1):

age indicates the age of the carrier in one-year increments; $age \in \{20, 21, \ldots, 85\}$. The maximum value is set to 85 years as no studies differentiate cancer risk for carriers older than this age.

surg indicates which surgeries a carrier has previously undergone; $surg \in \{None, BSO{<}40, BSO{=}40, BSO{=}41, \ldots, BSO{>}49, BM, BM\&BSO\}$. The age at BSO is saved for surgeries occurring between ages 40 and 50, as earlier removal of the ovaries reduces lifetime estrogen exposure, resulting in a lower breast cancer risk (Eisen et al. 2005).

bc indicates whether a carrier was previously diagnosed with breast cancer; $bc \in \{None, In\ treatment, {\leq}5\ years\ ago, {>}5\ years\ ago\}$. The carrier can have no history of breast cancer or currently be in treatment or in a posttreatment stage. The mortality rate for certain breast cancer subtypes (e.g., early stage triple negative) sharply drops after five years, and distant recurrences beyond five years after cancer treatment are rare (Lee et al. 2011). This variable indicates whether five or more years have passed since the completion of breast cancer treatment.

bcts indicates the breast cancer tumor stage at the time of diagnosis; $bcts \in \{None, I, II, III, IV\}$. As with most clinical studies, we distinguish between tumor stages, where stage I tumors are <2 cm and only in the breast, stage II tumors are 2–5 cm or spread to lymph nodes, stage III tumors are >5 cm or spread to the chest wall, and stage IV indicates cancer spread to other organs such as the liver, lungs, brain, or bones. A later stage at diagnosis indicates a less favorable prognosis and higher mortality rate (Edge and Compton 2010).

bcsu indicates the tumor subtype if breast cancer was diagnosed; $bcsu \in \{None, Luminal\ A, Luminal\ B, HER2, Triple\ Negative\}$. We use a standard breast cancer classification scheme, consisting of four molecular subtypes, which categorizes tumors based on common combinations of estrogen-, progesterone-, and HER2-receptor statuses (Sørlie et al. 2003). Triple negative and HER2-type tumors tend to be faster growing, leading to a later stage at diagnosis, higher rate of metastatic disease, and therefore higher mortality rate (Brown et al. 2008).

oc indicates whether a carrier was previously diagnosed with ovarian cancer; $oc \in \{None, In\ treatment, Post\text{-}treatment\}$. The carrier can have no history of ovarian cancer, currently be in treatment, or be posttreatment.

octs indicates the ovarian cancer tumor stage at the time of diagnosis; $octs \in \{None, I, II, III, IV\}$. Stage I tumors are contained within the ovaries or fallopian tubes, stage II tumors can have spread to the uterus or other pelvic organs, stage III tumors have spread to the abdominal lining or lymph nodes, and stage IV cancer has spread to other vital organs such as the spleen, liver, lungs, and others.

de indicates whether a carrier is alive, died from metastatic cancer, or died from other causes; $de \in \{Alive, Metastatic\ cancer\ death, Other\ death\}$.

One difference between the two cancers in our MDP model is the inclusion of a tumor subtype classification for breast cancer only. We make this assumption because of large differences in survival among breast cancer subtypes (e.g., five-year survival for stage III breast cancer is 48% if triple negative versus 85% if luminal A; Parise and Caggiano 2014). Available treatment options that target estrogen receptors (e.g., tamoxifen, aromatase inhibitors) or HER2 receptors (e.g., Herceptin) can significantly improve outcomes for breast cancer patients with certain subtypes (Hayes 2017). A large data set with outcomes for breast cancer

patients, by tumor stage and subtype, allows us to confidently construct transition probabilities in our model (Brown et al. 2008).

With ovarian cancer, tumor differences exist (e.g., serous versus nonserous cell types), but data are lacking about the distribution of subtype at stage of diagnosis (Bolton et al. 2012). Compared to breast cancer, ovarian cancer is one-tenth as prevalent in the general population, so there is less information available about long-term prognoses of ovarian cancer patients by both subtype and stage. We therefore only consider ovarian cancer stage at diagnosis in our model, as this clearly impacts long-term survival (Bolton et al. 2012).

Women diagnosed with triple negative breast cancer face an increased risk of recurrence and subsequent mortality for the first five years after treatment (Parise and Caggiano 2014), compared to other cancer subtypes. Additionally, following a BM as either preventive surgery or as part of breast cancer treatment, women report diminished quality of life for a longer period than after a BSO (Grann et al. 2010). For these reasons, we include the time since breast cancer diagnosis (≤ 5 *years ago*, >5 *years ago*) as a state variable, but this additional complexity is not warranted for ovarian cancer.

3.2. Action Space

The model's action space consists of four actions $A = \{W, BM, BSO, BM\&BSO\}$. If $surg = None$, indicating that no surgeries have been performed previously, a carrier can choose an action $a_t(s)$ from the following options: wait until the next period (W), undergo a bilateral mastectomy (BM), undergo a bilateral salpingo-oophorectomy (BSO), or undergo both procedures ($BM\&BSO$).

If $surg \neq None$, indicating that an organ has already been removed (either prophylactically or following a cancer diagnosis), the surgery corresponding to the removed organ is excluded from the future action space. Although women diagnosed with cancer ultimately decide whether to undergo a BM or BSO as part of treatment, we assume that treatment of breast cancer includes undergoing a BM, and treatment of ovarian cancer includes undergoing a BSO. These are reasonable assumptions for BRCA mutation carriers, as this is the standard of care because of the extremely high risk of developing a new cancer in the future (Trainer et al. 2010).

3.3. State Rewards and Transition Probabilities

An immediate reward, $r_t(s_t, a) \in [0, 1]$, is assigned to each state–action pair and deterministically determined by the carrier's health state at time t. If the action includes a surgery, this has either a temporary or lifelong impact on the state reward. If a carrier develops breast or ovarian cancer, the negative effect on the reward depends on the cancer stage. In each state, the minimum of the QOL factors corresponding to each state variable is chosen as the period reward. Therefore, cumulative QALYs are calculated by summing over all health states that are visited before death.

Let P_t denote the matrix of all transition probabilities at time t. The probability that a carrier transitions from state s_t to s'_{t+1} when choosing action a is denoted by $p_t(s'_{t+1} \mid s_t, a)$. Let $v^*(s_t)$ denote the optimal expected future reward when a carrier is in state s_t. Future rewards are discounted by a factor γ, $\gamma \in (0, 1)$. To find $v^*(s_t)$, we solve the Bellman equation (Puterman 2014):

$$v_t(s_t) = \max_{a \in A(s_t)} \left\{ r_t(s_t, a) + \gamma \sum_{s'_t \in S} p_t(s'_{t+1} \mid s_t, a) v_{t+1}(s'_{t+1}) \right\}, \quad \forall\, s_t \in S. \quad (1)$$

4. Solution Approach

The full model described in Section 3 consists of eight state variables, each assuming at least three possible values—resulting in more than four million possible states—and the action set contains up to four actions, making an analytical solution infeasible because of the problem complexity. In the following sections, we first describe structural analysis of a limited problem scope, and then we convert the full model to a linear program to find the optimal policy numerically.

4.1. Structural Properties

The size of the complete state space imposes the "curse of dimensionality," making a DP-based solution intractable. To better understand the structural properties of our MDP model, we consider a narrower problem scope with one cancer type and one surgery. We analytically derive an optimal control limit policy for two versions of this simplified problem: a patient has already undergone a BM or BSO and is considering the other surgery. This scenario reflects the decision faced by BRCA mutation carriers who previously underwent prophylactic surgery or cancer treatment.

The complete analyses including all required assumptions, propositions, theorems, and proofs are given in Appendix B.

Our analysis extends the work of Chhatwal et al. (2010) by showing that a threshold policy exists for patients previously diagnosed with breast or ovarian cancer (and who thus underwent a BM or BSO, respectively), who must still decide whether and when to undergo the other surgery (BSO or BM, respectively). One challenge with such a formulation is converting a multidimensional state space into a single-dimensional vector. Our proposed solution is to define a revised state space, essentially according a carrier's risk of death. In this way, state transitions only occur from a "better" health state to a "worse" state, prohibiting a carrier from moving back to a healthier state again.

We first consider a breast cancer survivor and present the reverse scenario for an ovarian cancer survivor thereafter. The structural analysis requires the following mild assumptions: the annual risk of ovarian cancer is nondecreasing as a carrier ages; quality of life and future remaining QALYs are nonincreasing with age; quality of life decreases after surgery or if ovarian cancer develops; and QALYs following an ovarian cancer diagnosis are lower than with prophylactic surgery. Under the above assumptions, we show that there is a threshold age $\bar{s} \in \{x^{20}, x^{21}, \ldots, x^{85}\}$, such that for female BRCA mutation carriers younger than $\bar{s}$, it is not optimal to undergo prophylactic surgery, whereas for women older than $\bar{s}$ it is optimal to undergo surgery. We demonstrate that such a threshold policy exists for both populations (breast cancer and ovarian cancer survivors). This analysis complements the numerical solution presented in Section 5 by showing that in these specific circumstances, surgery is always optimal when the remaining cancer risk is sufficiently high.

4.2. Solution via Linear Programming

Most of the states within our MDP model have a limited number of successor states, resulting in a sparse transition matrix. Solving the problem in Equation (1) through value iteration would require calculating the value of all states, most of which are never visited. We exploit the sparsity of the transition matrix to solve the MDP using linear programming, a standard approach (White and White 1989, de Farias and van Roy 2003) that would be computationally difficult for nonsparse matrices (Puterman 2014).

To obtain an exact solution via LP, we first convert our finite-horizon MDP to an infinite-horizon model. Following the approach given by Powell (2011), we take the limit

$$v(s) = \lim_{t\to\infty} v_t(s_t) \tag{2}$$

and obtain a revised model formulation:

$$v(s) = \max_{a\in A}\left\{r(s,a) + \gamma \sum_{s'\in S} p(s' \mid s,a)v(s')\right\}, \quad \forall\, s \in S. \tag{3}$$

Under the infinite-horizon MDP model, the probability that a carrier older than T eventually arrives to an absorbing state (*other death*) is essentially 100% because the age-related mortality rate monotonically increases. Hence, we do not expect significant differences between the finite- and infinite-horizon versions, as the immediate reward $r(s,a)$ for a state indicating death is zero.

At optimality, $v^*(s)$ is the smallest value of $v(s)$ that satisfies the following inequality:

$$v(s) \geq \max_{a\in A}\left\{r(s,a) + \gamma \sum_{s'\in S} p(s' \mid s,a)v(s')\right\}. \tag{4}$$

To find $v^*(s)\ \forall\, s \in S$, we minimize $v(s)\ \forall\, s \in S$, while including Equation (4) as a constraint for every state–action pair. We therefore obtain the following linear program:

$$\min_{v} \sum_{s\in S} v(s) \tag{5}$$

$$\text{subject to } v(s) \geq r(s,a) + \gamma \sum_{s'\in S} p(s' \mid s,a)v(s'), \quad \forall\, s \in S, a \in A. \tag{6}$$

The LP formulation of the full MDP model given in Section 3 has $|S| = 4{,}387{,}500$ decision variables and $|S| \times |A| = 7{,}775{,}625$ constraints. The program is implemented in Matlab R2015b and solved by Gurobi 6.5.1.

After solving for the optimal state values, $v^*(s)$, the corresponding optimal policy, π^*, that satisfies (3) is determined by

$$\pi^*(s) = \arg\max_{a\in A}\left\{r(s,a) + \gamma \sum_{s'\in S} p(s' \mid s,a)v(s')\right\}. \tag{7}$$

Table 1. Average Life Expectancy, Survival Probability, and Cumulative Risk of Breast and Ovarian Cancer Under Different Decision Policies

Mutation	Decision policy	Average life expectancy (years)	Survival prob. by age 85 (%)	Cumulative cancer risk by age 65 (%)	
				Breast	Ovarian
BRCA1	No prophylactic surgery	69.8	60.0	49.8	30.3
	No surgery before age 50	72.7	68.5	31.3	15.9
	Only BM at age 30	73.0	70.6	7.3	30.8
	Only BSO at age 30	75.3	77.1	25.6	8.3
	BM and BSO at age 30	77.3	83.8	5.1	8.2
	QALY-maximizing	76.9	81.8	5.6	9.5
BRCA2	No prophylactic surgery	75.5	77.5	40.0	11.5
	No surgery before age 50	76.5	80.0	34.5	5.0
	Only BM at age 30	77.5	83.4	5.6	11.2
	Only BSO at age 30	78.1	84.4	19.7	2.5
	BM and BSO at age 30	79.2	87.7	3.5	2.6
	QALY-maximizing	78.0	84.2	10.2	4.4

5. Numerical Study

Although we determine optimal threshold policies for two simplified versions of the model where a BRCA mutation carrier is only considering one surgery type (Appendix B, Theorems 1 and 2), these do not capture the complexity of the full model with multiple surgery options (Section 3). In particular, the benefits of a prophylactic BSO on breast cancer risk are not included in the analytical solution. We therefore show numerical solutions for the full model (Table 1) to provide insights into optimal surgery timing and sequence under different assumptions.

To test the robustness of the optimal policy, we conduct various sensitivity analyses. We vary the duration and magnitude of a surgery's impact on a carrier's quality of life. To reflect potential decisions faced by different BRCA mutation carriers, we restrict the minimum eligible age for a BSO (i.e., to capture a carrier's preference to delay the surgery until after child bearing) and include a constraint for whether a patient prefers to never undergo a bilateral mastectomy. We also examine the optimal strategy after either a prior breast or ovarian cancer diagnosis, to provide comparison with our analytical results. Finally, we consider variations in breast and ovarian cancer risk and surgery efficacy at reducing these risks, reflecting uncertainty in the medical literature, as well as changes in mortality rates postcancer to account for potential future advances in medical treatment. Our model validation process is outlined in Appendix D.

5.1. Data Sources

The model's transition probabilities and rewards are based on values obtained from published clinical studies. We use BRCA1- and BRCA2-specific values whenever possible. If multiple data sources are available, we select those with greater sample sizes and the most recent studies to reflect the latest advances in cancer therapy.

For the baseline risk for breast and ovarian cancer we use a large meta-analysis (Chen and Parmigiani 2007). Key probability estimates are summarized in Table 2 and include age-dependent breast and ovarian cancer risk, distribution of cancer by stage and subtype (breast cancer only), and cancer risk reduction following a prophylactic BM or BSO. Cancer-specific mortality rates are given in Table 3, and age-dependent mortality rates from other causes are obtained from published sources (CDC 2014). To reflect current practices in medical treatment, no studies older than 2010 are considered for mortality rates. Quality of life values for each health state are presented in Table 4. Unless stated otherwise, the model's objective is to maximize a carrier's discounted lifetime QALYs. In the results, we give average life expectancy (in years), probability of surviving to age 85, and cumulative probabilities of

Table 2. Distributions of Cancer Subtypes, Stages, and Risk Reduction of Prophylactic Surgeries

Parameter	BRCA1	BRCA2	Source
Breast cancer subtype			
Luminal A	0.043	0.100	Mavaddat et al. (2012)
Luminal B	0.216	0.717	
HER2	0.056	0.026	
Triple negative	0.685	0.157	
Breast cancer stage at diagnosis			
Luminal A/B			
I	0.493		Brown et al. (2008)
II	0.402		
III	0.074		
IV	0.031		
HER2			
I	0.293		
II	0.462		
III	0.179		
IV	0.066		
Triple negative			
I	0.338		
II	0.497		
III	0.122		
IV	0.043		
Ovarian cancer stage at diagnosis			
I	0.124	0.095	Bolton et al. (2012)
II	0.104	0.056	
III	0.640	0.733	
IV	0.132	0.116	
Breast cancer risk reduction with BM (HR)			
BM only	0.09 (0.02, 0.38)*		Rebbeck et al. (2004)
BM & BSO	0.05 (0.01, 0.22)*		
Breast cancer risk reduction with BSO (OR)			
≤40 years	0.41 (0.25, 0.68)*		Eisen et al. (2005)
40–50 years	interpolated		
≥50 years	0.70 (0.24, 2.03)*		
Ovarian cancer risk reduction with BSO (HR)	0.21 (0.12, 0.39)*		Rebbeck et al. (2009)

Notes. HR, Hazard ratio (a ratio of the rate of developing cancer with and without prophylactic surgery); OR, odds ratio (a ratio of the odds of developing cancer with and without prophylactic surgery).
*95% confidence interval.

breast and ovarian cancer, based on a simulation of our underlying MDP model with 20,000 iterations.

5.2. QALY-Maximizing Surgery Sequence

5.2.1. BRCA1. Under our baseline parameter values (Tables 2–4), the QALY-maximizing policy for BRCA1 carriers is to undergo a BM between ages 30 and 60, as depicted in Figure 1. Before age 30, the risk of breast cancer is not sufficiently great enough—only about 1% of BRCA mutation carriers develop breast cancer before age 30 (Chen and Parmigiani 2007)—to justify the immediate loss in quality of life resulting from a BM. Beyond age 60, a carrier's future breast cancer risk is not great enough to justify a BM—assuming that she has chosen to undergo a BSO by then—because a BSO acts a partial substitute to a BM by also reducing breast cancer risk. However, if a carrier elects to *not undergo* a BSO, then a BM is warranted after age 60 because her future risk of developing breast cancer after age 60 is around 20% (Chen and Parmigiani 2007). In other words, undergoing a BM incurs a "fixed cost" because we assume a five-year decrement to quality of life, which must be amortized over a sufficient number

Table 3. Cancer-Specific Mortality Rates

Tumor subtype and stage	Annual mortality rate BRCA1	BRCA2	Source
Breast cancer			
Luminal A[a]			
Stage I	0.004		Parise and Caggiano (2014)
Stage II	0.012		
Stage III–IV	0.041		
Luminal B			
Stage I	0.008		
Stage II	0.026		
Stage III–IV	0.074		
HER2			
Stage I	0.011		
Stage II	0.037		
Stage III–IV	0.099		
Triple negative			
Stage I	0.015		
Stage II	0.047		
Stage III–IV	0.147		
Ovarian cancer			
Stage I–II	0.06	0.04	Bolton et al. (2012)
Stage III–IV	0.14	0.10	

[a]Breast cancer subtypes luminal A and luminal B (HER2 negative) from Parise and Caggiano (2014) are combined into luminal A, to match the subtype definition used by Sørlie et al. (2003).

of years in the form of reduced breast cancer risk to warrant the up-front cost.

The optimal policy also recommends that any female BRCA1 carrier over age 40 undergo a BSO (Figure 1), because her future risk of developing ovarian cancer is sufficiently high to justify the expected reduction in quality of life. In particular, the future risk of a BRCA1 carrier developing ovarian cancer after age 40 is around 40%, which comprises nearly all of her lifetime risk, as the probability of ovarian cancer before age 40 is only 2%–3% (Chen and Parmigiani 2007). The BSO surgery is recommended until age 85, as the short-term impact on quality of life (a decrement of 0.05 for one year; Grann et al. 2010) in postmenopausal women over age 50 is modest, compared to the sizable risk reduction in cancer risk (approximately 30% reduction in breast cancer risk (Eisen et al. 2005) and 80% reduction in ovarian cancer risk (Rebbeck et al. 2009)).

After solving for the optimal policy, we apply our MDP model to simulate average life expectancy and breast and ovarian cancer incidence under different prophylactic surgery policies (Table 1). The QALY-maximizing prophylactic surgery sequence for a healthy (i.e., no breast/ovarian cancer history) BRCA1 carrier generates a life expectancy of 76.9 years, compared to 69.8 years if she opts for no prophylactic surgery, a gain of more than 7 years, on average. If a woman chooses to delay both surgeries until after age 50, her projected life expectancy is 72.7 years. Although life expectancy increases by 0.4 years if both surgeries are performed very early at the age of 30, cumulative QALYs are lower with early surgeries. The QALY-maximizing sequence

Table 4. Baseline Quality of Life Values of Each Health State

Health state	QOL factor	Impact duration	Source
Breast cancer			
Stage I–III	0.87	1 yr	Grann et al. (2010)
Stage IV (de novo)	0.59	Lifetime	Grann et al. (1999a)
Stage IV (recurrence)			
Luminal A	0.59	2.2 yr	Grann et al. (1999a),
Luminal B	0.59	1.6 yr	Lobbezoo et al. (2015)
HER2	0.59	1.3 yr	
Triple negative	0.59	0.7 yr	
Ovarian cancer			
Stage I–III	0.84	1 yr	Grann et al. (2010)
Stage IV (de novo)	0.59	Lifetime	Grann et al. (1999a)
Stage IV (recurrence)	0.59	2.5 yr	
Surgery			
BM	0.88	5 yr	Grann et al. (2010)
BSO	0.95	Constant until age 50, 1 yr after age 50	

Notes. De novo, Patient is found with stage IV cancer at diagnosis; recurrence, patient progressed from stage I, II, or III to stage IV.

balances this trade-off of survival gain with early surgery against diminished QOL for the carrier following a BM and BSO. Figure 1 depicts the optimal surgery sequence for every age ranging from 20 to 85 years old.

For BRCA1 mutation carriers, the cumulative risk of breast cancer by age 65 decreases from 49.8% with no prophylactic surgery to 5.6% under the QALY-maximizing policy, as illustrated in Figure 2. Similarly, ovarian cancer risk decreases from 30.3% with no prophylactic surgery to 9.5% under the QALY-maximizing policy. Note, the cumulative risk of ovarian cancer does not depend on whether a carrier undergoes a BM; hence, there are only three projected curves for ovarian cancer. Although cancer risk is slightly higher than with the more aggressive policy of undergoing both surgeries at age 30 (breast cancer risk of 5.1%, ovarian cancer risk of 8.2%), the QALY-maximizing policy provides an estimated 94%–98% of the cancer-reducing benefits of a more aggressive, early surgery policy, but it considers both the overall quality of life and survival gains from such drastic surgeries. Nevertheless, carriers who wish to minimize cancer risk as much as possible may prefer to undergo a BM or BSO at an earlier age.

5.2.2. BRCA2. For BRCA2 mutation carriers, the optimal policy delays both surgeries because of the lower overall risk of breast and ovarian cancer, compared to BRCA1 carriers. With no prophylactic surgery, our model's simulation projects that approximately 40% of BRCA2 carriers develop breast cancer by age 65, compared to 50% of BRCA1 carriers; additionally, 12% of BRCA2 carriers develop ovarian cancer by age 65, significantly less than the 30% risk faced by BRCA1 carriers (Table 1). Our simulation results are generally consistent with a large meta-analysis of BRCA mutation carriers (Chen and Parmigiani 2007).

Undergoing a BM is recommended for BRCA2 carriers aged 40 to 46 years (Figure 1). After age 46, the reduction in future risk of breast cancer (assuming a carrier has remained cancer-free until age 46) does not offset the QOL loss imposed by a prophylactic BM. However, a BSO is recommended starting at age 50 and after, as women are assumed to enter natural menopause around this age; thus, the QOL decrement after a BSO is limited.

Under the QALY-maximizing surgery sequence, life expectancy is 78.0 years compared to 75.5 years with no cancer-preventive surgeries, a smaller overall gain than for BRCA1 carriers because the overall risk of cancer is lower. Thus, the marginal benefits of undergoing prophylactic surgery are more modest for BRCA2 carriers. As with BRCA1, the QALY-maximizing policy results in a higher incidence of breast cancer compared with a strategy of undergoing both a BM and BSO at age 30, because the QALY-maximizing policy recommends a BM only for a limited group of carriers aged 40 to 46. The risk of ovarian cancer by age 65 is reduced from 11.3% to 4.6%, slightly higher than the 2.4% risk if both surgeries occur at age 30.

5.3. Sensitivity Analysis

To test model robustness, we vary model parameters to reflect patient heterogeneity, uncertainty in efficacy, and future advances in cancer treatment, as discussed below. For each scenario, we solve for the new optimal policy and simulate health outcomes over 20,000 iterations. Additional sensitivity analysis results are given in Appendix E.

5.3.1. Quality of Life Estimates. Variability exists in QOL estimates following prophylactic surgery among women at high risk of developing cancer, as highlighted by Grann et al. (2010). These variations are largely attributable to differences in study populations (e.g., mutation carriers, cancer survivors, healthcare professionals) or methodologies for eliciting preferences.

As both surgeries impact physical and psychological well-being, we examine how different assumptions regarding QOL, reflecting different patient preferences, affect the optimal surgery sequence. For BRCA1 carriers, reducing the impact of a BM on QOL by one-half would expand the window to undergo the surgery to age 77 (Figure 3). Similarly, reducing the impact of a BSO on QOL by one-half flips the sequence of surgeries, recommending BSO starting at age 30 followed by BM from age 40 to 60. When varying the impact of both surgeries, results demonstrate that the optimal surgery timing is more sensitive to QOL following BM. For example, if a BM has a more detrimental impact on quality of life (QOL = 0.5), then the optimal strategy for women aged 30 to 39 is to instead undergo a BSO, to reduce the risk of breast cancer (and the subsequent need to undergo a BM as part of cancer treatment).

Figure 1. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Who Have Not Previously Had Breast or Ovarian Cancer or Undergone Prophylactic Surgery

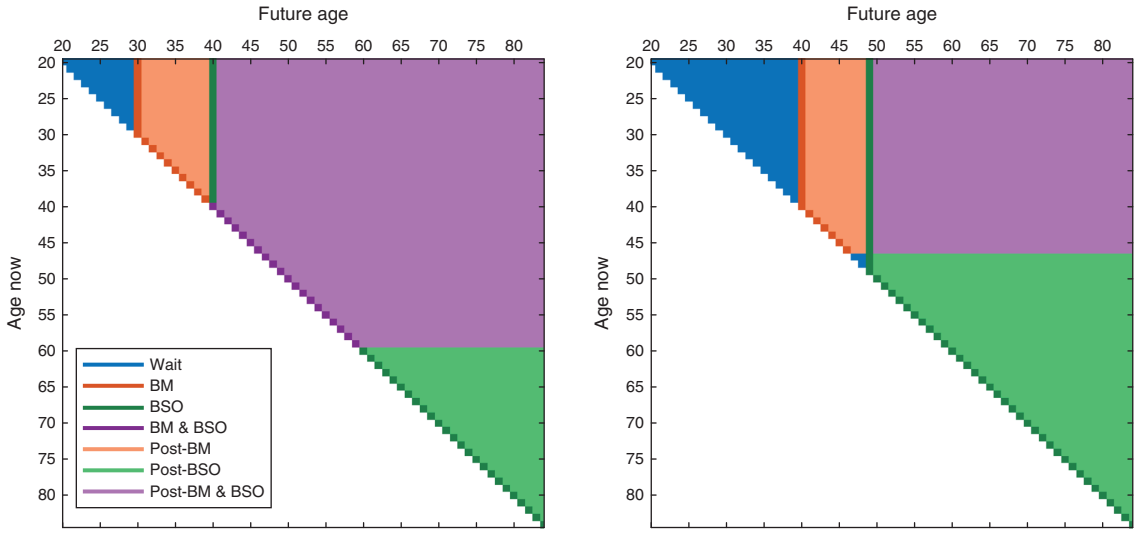
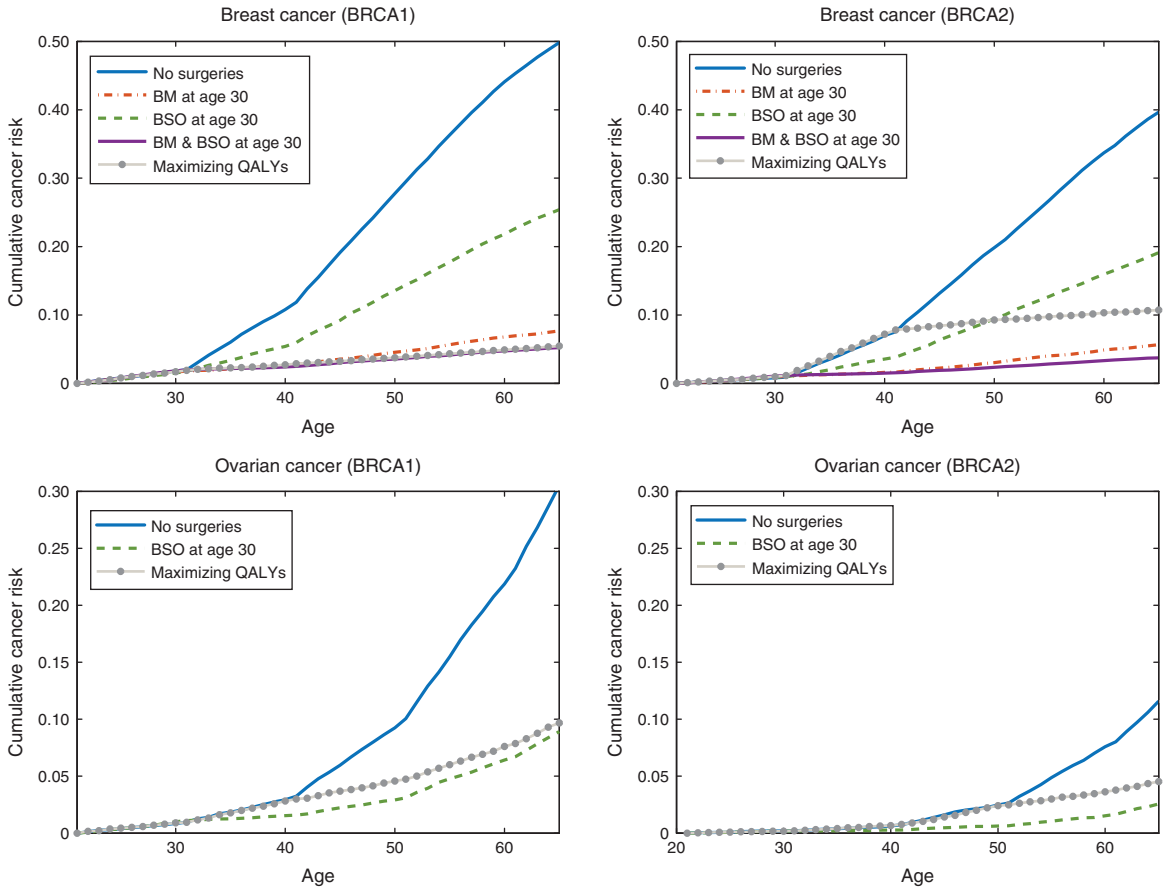


Figure 2. Cumulative Cancer Risk Under Different Surgery Sequences



For BRCA2 carriers, we find qualitatively similar results. Assuming the impact of BM on QOL decreases by half, the optimal age to begin undergoing the surgery is lowered from 40 to 30. Similarly, reducing the impact of a BSO by one-half lowers the starting age of a recommended BSO from 50 to 40, and the optimal surgery sequence does not include a BM at any age because much of the breast cancer risk is already reduced by the BSO (Figure 4).

5.3.2. Prior Cancer Diagnosis. Some BRCA mutation carriers might consider a limited set of surgery options, either because of personal preferences or a prior cancer diagnosis that required one of the surgeries to be previously performed as part of treatment (Trainer et al. 2010). Following a diagnosis of ovarian cancer, a BSO will typically occur as part of treatment. This surgery confers additional benefit by reducing subsequent breast cancer risk; therefore, undergoing a BM is no longer QALY maximizing at any age, assuming the carrier follows routine breast cancer screening guidelines.

Similarly, the secondary benefits offered by a BSO in reducing breast cancer risk are negligible to those carriers who have previously undergone a bilateral mastectomy. Among young breast cancer survivors who have already undergone a BM, the optimal window to subsequently undergo a BSO is postponed to age 46 (BRCA1) or age 48 (BRCA2). Beyond these ages, it is always QALY maximizing to perform a BSO, numerically in line with Theorem 2, which states that performing a surgery is always optimal when the carrier's age (which is proportional to cancer risk) exceeds the optimal control threshold $\bar{s}_t$.

To further illustrate this analysis, suppose a carrier is diagnosed with breast cancer at the age of 35 and undergoes a BM as part of treatment. If she elects to not undergo any additional prophylactic surgery, her life expectancy is approximately 67 years (BRCA1) or 71 years (BRCA2), averaged across all breast cancer subtypes and stages. However, if she decides to subsequently undergo a BSO at the QALY-maximizing recommended age, her life expectancy increases to 70 years (BRCA1) or 72 years (BRCA2). Her ovarian cancer risk by age 65 is reduced from 30.1% to 11.2% (BRCA1) or from 11.5% to 4.1% (BRCA2) with this strategy.

5.3.3. Improved Breast Cancer Screening or Treatment. Routine screening for ovarian cancer, unfortunately, has very limited accuracy at detecting cancerous tumors (van Gorp et al. 2011). As a result, nearly 80% of ovarian cancers are diagnosed late, at stage III or IV (Bolton et al. 2012), compared to only 12% of breast cancers (Brown et al. 2008). Frequent mammography and MRI may be effective alternatives to surgery for BRCA mutation carriers to decrease breast-cancer-specific mortality, although efforts to improve screening adherence among high-risk women are needed (Garcia et al. 2014). Enhanced screening will not *prevent* cancerous tumors from developing; however, it allows for earlier detection and treatment, improving prognosis and survival.

Our baseline parameter assumptions reflect current breast cancer screening practices among BRCA mutation carriers, including the distribution of tumor stages that patients present at diagnosis (Table 2). We examine how changes in breast cancer screening rates affect the optimal surgery sequence, under the optimistic assumption that breast cancer is always diagnosed at stage I. Compared to the original optimal policy, the model recommends a less radical surgery sequence (Figure E.1): BSO at age 39 (BRCA1) or age 49 (BRCA2), and no BM at any age (both BRCA1 and BRCA2). In this case, the probability of a breast cancer diagnosis by age 65 in a BRCA1 carrier increases to 29.5% from 5.6% (under the original optimal policy), with a reduction in life expectancy of 0.9 years. Under similar screening conditions for BRCA2 carriers, the probability of developing breast cancer reaches 33.3%, with a decrease in life expectancy of less than 0.1 years. Although this scenario would require complete adherence to the screening schedule and essentially perfect screening accuracy via breast mammography and/or MRIs, this analysis demonstrates how improved screening acts as a partial substitute for a prophylactic mastectomy surgery.

Women who develop certain breast cancer subtypes, especially triple negative, experience poorer prognoses as these tumors do not respond to some therapies (e.g., tamoxifen or Herceptin) that target growth receptors (Parise and Caggiano 2014). Although TN tumors represent only 15% of breast cancers in the general population, this subtype is much more common in BRCA1 carriers, accounting for 70% of all tumors. If medical advances improve treatment of TN cancers, leading to survival outcomes comparable to luminal A

Figure 3. Sensitivity Analysis for Postsurgery Quality of Life Among BRCA1 Carriers

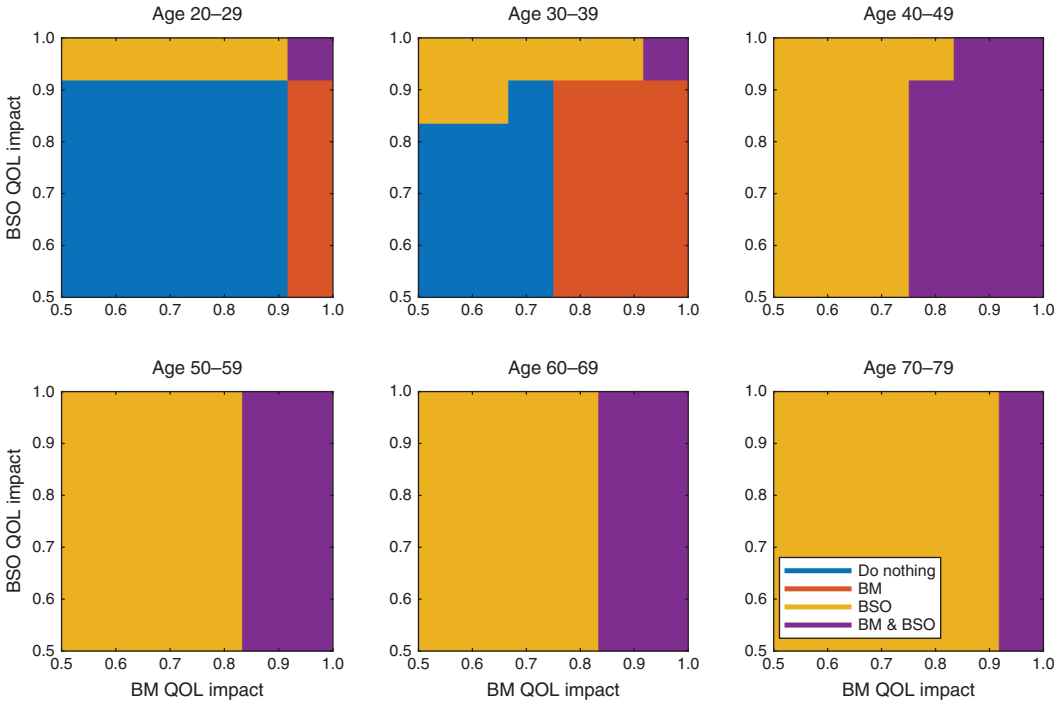
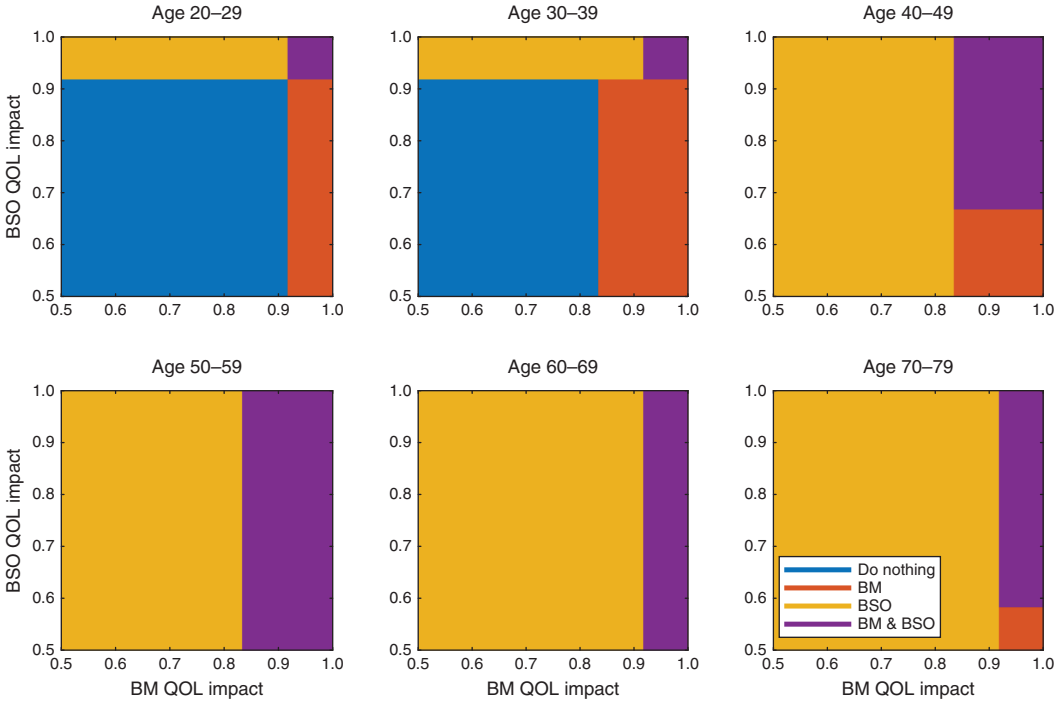


Figure 4. Sensitivity Analysis for Postsurgery Quality of Life Among BRCA2 Carriers



tumors, our model projects that average life expectancy in BRCA1 carriers will increase by 0.1 years. This minimal improvement occurs because the optimal policy does not change (Figure E.2); in other words, even with survival gains following TN breast cancer, it is still QALY maximizing to undergo a BM between ages 30 and 59. Under this scenario, there is less benefit for BRCA2 carriers, as only 15% of tumors are a TN subtype.

5.3.4. Fertility Considerations. Some women may prefer to delay prophylactic surgery until a later age, especially a BSO, as the procedure eliminates the ability to have biological children. They may instead wish to complete family planning or wait until the natural onset of menopause. As our model with baseline parameters recommends undergoing a BSO at age 40 (BRCA1) or 50 (BRCA2), most women will not be substantially constrained in their family planning decisions through this recommendation.

Suppose a BRCA1 carrier optimally undergoes a bilateral mastectomy at age 30, but delays ovary removal until age 50 (Figure E.3). In this case, her lifetime ovarian cancer risk increases (relatively) by 60% (from 9.5% to 15.6%)—significantly decreasing life expectancy by 1.2 years, on average—compared to the QALY-maximizing policy. Conversely, for BRCA2 carriers, the added constraint of delaying a BSO until age 50 is nonbinding, so there is no impact on life expectancy relative to the optimal policy.

5.3.5. Constrained Surgery Options. In addition to postponing ovary removal to preserve their fertility, some carriers may also wish to delay having a bilateral mastectomy. If a BRCA1 carrier waits until after age 50 to undergo both procedures, she still improves overall survival compared to having no prophylactic surgery, although she would lose 4.2 years of life expectancy compared to the QALY-optimal policy (Table 1). On the other hand, if a BRCA2 carrier chooses to wait until after age 50 to undergo either surgery, then only a BSO is recommended, since her remaining breast cancer risk is not sufficiently high to warrant a BM, assuming she continues to undergo breast cancer screening (Figure E.4). However, her life expectancy would drop by 1.5 years compared to the optimal policy (Table 1).

If a carrier chooses for personal reasons to *never* undergo a prophylactic bilateral mastectomy, then her average life expectancy is 2.3 years (if BRCA1) or 0.5 years (if BRCA2) shorter than under the QALY-maximizing policy. In this case, our model recommends undergoing a BSO starting at age 40 (for both BRCA1 and BRCA2 carriers) because of its substantial benefits at reducing breast cancer risk (Figure E.5).

5.3.6. Surgery Efficacy. Reductions in breast or ovarian cancer risk following prophylactic surgery are typically estimated from retrospective studies of several hundred female BRCA mutation carriers, in part because it would now be considered unethical to randomize BRCA mutation carriers to less effective treatment arms (Rebbeck et al. 2009, 2004; Eisen et al. 2005). Nevertheless, individual patient heterogeneity exists, potentially due to mutation genotype, surgeon practices, or other individual risk factors. We therefore consider wide variations in risk reduction parameters by assuming values ranging from the upper to lower 95% confidence intervals (Table 2), holding all other parameters constant.

In general, if a BM confers a greater reduction in breast cancer risk, then the optimal age to undergo this procedure is largely unaffected—primarily because the procedure is already very effective in our baseline assumptions—although the remaining lifetime risk of breast cancer drops by half (from 5.6% to 2.9%) for BRCA1 carriers (Figure E.6). Conversely, under the pessimistic assumption that a BM reduces breast cancer risk by only 60%, then it is better for BRCA1 carriers to delay the BM surgery until ages 48 through 55, and for BRCA2 carriers to never undergo the procedure (Figure E.7). Although most medical studies are in agreement that the risk reduction for breast cancer following a bilateral mastectomy is likely higher than 60% (Rebbeck et al. 2004, Hartmann et al. 2001), our results are consistent with what we might expect.

Breast cancer risk is also reduced after ovary removal, with the benefit diminishing as a woman elects to undergo surgery at an older age—i.e., breast cancer risk is thought to be proportional to cumulative estrogen and progesterone exposure (Toniolo et al. 1995, Missmer et al. 2004). Interestingly, if the breast cancer risk reduction following a BSO is much higher than initially assumed (approximately 75% at any age), then we find that women should instead undergo a BSO

at age 30 (if BRCA1) or age 40 (if BRCA2) and never undergo a BM (Figure E.8). In this case, average life expectancy is similar to that under the original optimal policy. On the other hand, if breast cancer risk reduction following a BSO is much lower than initially assumed, then the optimal age to undergo a BM increases to ages 30 and up (if BRCA1) or ages 40 to 77 (if BRCA2) (Figure E.9). In this case, it is important for women to also undergo a BM to offset the loss because a BSO confers less breast cancer risk reduction.

Finally, if ovarian cancer risk following a BSO is reduced by about 90%, the upper limit from a large meta-analysis (Rebbeck et al. 2009), the optimal policy does not significantly change (Figure E.10). However, if a BSO is less effective at reducing ovarian cancer risk, then BRCA1 carriers should delay undergoing a BSO until age 48 or later, resulting in a life expectancy that is 1.9 years shorter, on average, compared to the original optimal policy (Figure E.11). Since BRCA2 carriers already wait until age 50 to undergo a BSO, there is no change in their optimal policy.

5.3.7. Mortality Rates. We also examine variations in mortality rates following both cancer types (Table 3). If breast-cancer-related mortality rates are 20% higher than initially assumed, life expectancy decreases only slightly, assuming that women still elect to undergo prophylactic surgery (Figure E.12). On the other hand, a 20% decrease in breast cancer mortality leads to a very different optimal policy, essentially splitting the BRCA1 population into four groups (Figure E.13): women younger than 36 have more future years to benefit from a BM so it is still optimal to undergo a BM; women aged 36 to 41 should only undergo a BSO because this also reduces breast cancer risk; women aged 42 to 56 should undergo both procedures because the benefits of a BSO decline so a BM is also warranted; and women aged 57 and older should undergo only a BSO, as there are not enough future years to justify undergoing a BM.

For ovarian cancer, a 20% increase (or decrease) in mortality rates decreases (or increases) life expectancy by 0.3 years, on average, assuming women continue to chose the optimal policy (Figures E.14–E.15). This smaller difference is due to the lower overall risk of ovarian cancer in both BRCA1 and BRCA2 carriers.

6. Discussion

This paper presents a comprehensive approach to determine a recommended course of action for BRCA1/2 mutation carriers deciding whether and when to undergo cancer risk-reducing prophylactic surgery. Our study develops a novel Markov decision process model of two simultaneous diseases—and multiple actions that can reduce the incidence of one or both diseases—an advance not previously explored in the decision modeling literature. Our study combines an MDP model with a carefully appraised set of parameters based on observed clinical data. Although the size of the state space exceeds four million states, we are able to exploit the sparsity of the transition probability matrix and find an exact optimal solution using linear programming.

Female carriers of a BRCA genetic mutation are at substantially increased risk of breast and ovarian cancer compared to the general population. Our primary numerical findings indicate that to maximize a BRCA1 carrier's lifetime quality-adjusted life years, a bilateral mastectomy is recommended between ages 30 and 60, along with a bilateral salpingo-oophorectomy from age 40 onward. Under this sequence, our model computes an average life expectancy of 77 years for a 20-year old BRCA1 carrier, a 10% increase compared to performing no prophylactic surgeries. Results differ for BRCA2 carriers, with a later recommended age to undergo surgery, as the annual risk of developing breast or ovarian cancer is lower compared to that for BRCA1 carriers.

Individual preferences about the impact of prophylactic surgeries on a carrier's quality of life can vary, and we provide sensitivity analysis demonstrating how the QALY-maximizing sequence changes when each individual surgery triggers a higher or lower impact on QOL. Results show that surgery schedules are more sensitive to changes in the QOL impact of a BM than a BSO. The actress and BRCA1 mutation carrier Angelina Jolie—whose public discussion of her surgery choices greatly increased awareness about BRCA—chose to undergo a BM at age 38 and BSO in her early 40s. Under our model's baseline assumptions, her personal surgical decisions are in line with our model's recommended surgery sequence.

The model's optimal policy is sensitive to several key assumptions, most notably to baseline breast cancer

screening adherence, lifetime risks of breast and ovarian cancers, and each surgery's effectiveness at reducing cancer risk. The model's objective is to maximize lifetime QALYs, which incorporates adverse effects of such aggressive prophylactic surgeries. If a woman chooses another objective, such as maximizing survival probability up to a certain age, then the recommended age to undergo cancer-preventive surgery might differ. One surprising finding is that other modeling assumptions, including BSO surgery delay due to fertility considerations and survival rates following treatment of triple negative breast cancer, have minimal to no impact on the QALY-maximizing surgery sequence.

In contrast to Abdollahian and Das (2015), who find that the QALY-optimal policy for BRCA1 carriers is to first undergo a prophylactic BSO at age 30 and then BM at age 50, we find essentially the reverse policy: undergo BM at age 30 and delay BSO until age 40 or later. We note several key differences between their study and ours, which may partially explain our different findings. First, in their MDP formulation, Abdollahian and Das (2015) assume that breast and ovarian cancer are both absorbing states—precluding the development of the *other* cancer—despite clinical studies suggesting that this indeed occurs. In particular, Metcalfe et al. (2005) estimate that 13% of BRCA1 and 7% of BRCA2 carriers develop ovarian cancer within 10 years of a breast cancer diagnosis, assuming the carrier does not undergo a prophylactic BSO. Our MDP formulation allows for both breast and ovarian cancer patients to potentially develop the other cancer, in addition to incorporating reduced life expectancy resulting from metastases of the original cancer.

A second difference is that Abdollahian and Das (2015) assume that 79% of breast cancer tumors are estrogen-receptor positive (ER+), whereas we assume that 26% of tumors in BRCA1 carriers are ER+ (corresponding to luminal A/B subtypes), consistent with other clinical studies (Mavaddat et al. 2012). The distribution of tumor subtypes impacts survival probabilities, as ER-negative tumors (i.e., HER2 and triple negative subtypes) tend to have worse prognoses, and BRCA1 carriers are particularly susceptible to these subtypes. Given these estimates, the recommendation by Abdollahian and Das (2015) to wait for a BM until age 50 may be considered too risky. Third, they assume that only 47% of breast cancers remain "local" (i.e., stage I or II) based on a study of patients from 1975 to 1981 (Kurian et al. 2010). In contrast, we assume that 87% of tumors are diagnosed at stage I or II based on a more recent cohort in California from 2004, which better reflects advances in early detection due to mammography (Brown et al. 2008). Fourth, Abdollahian and Das (2015) assume a single state for ovarian cancer, whereas we provide a distribution of stages I, II, III, and IV, conditional on BRCA1/2 mutation status (Bolton et al. 2012). With 75%–85% of ovarian cancer tumors diagnosed as stage III or IV—predominantly because of poor screening technology—this assumption significantly impacts postcancer survival estimates. Moreover, ovarian cancer very rarely develops in BRCA mutation carriers under age 40 (Chen and Parmigiani 2007), so recommending a BSO at age 30, with its associated impact on fertility and quality of life in young women, may be too aggressive for most women. Finally, Abdollahian and Das (2015) assume lower quality of life estimates (0.76 after BM; 0.82 after BSO) compared to ours (0.88 for 5 years after BM; 0.95 after BSO), which are commensurate with studies of cancer-related quality of life (Tengs and Wallace 2000). Collectively, these differences in model structure and parameter assumptions may explain our different results.

6.1. Limitations

As with any stylized mathematical model of an underlying disease process, our MDP model has several limitations. We select an appropriate state space to reflect key differences in transition probabilities, mortality, surgery efficacy, and postsurgery quality of life to ensure tractability in obtaining an optimal solution. Of course, this necessarily simplifies the complex tumor development and progression process, and nuances in different treatment regimens.

With only one in 400 to 800 women carrying a BRCA mutation, many of whom are unaware of their status, most clinical studies involving BRCA mutation carriers typically include small samples, often limiting the explanatory power of the data. We therefore are not able to obtain BRCA1- or BRCA2-specific estimates of the risk-reducing effects of surgeries. Although the baseline cancer risk varies between mutation types, the underlying mechanisms generating the risk reductions are likely similar for both mutation types, enabling us

to use the same parameter values. Cancer-specific mortality rates are typically aggregated at 5- or 10-year intervals, leading us to assume a constant mortality rate after diagnosis.

Structural limitations include a static breast cancer screening policy and the omission of a local recurrence (to the breast or ovary) and other treatment options. Although the quality of breast cancer screening and adherence to the recommended schedule varies from woman to woman, we assume a constant screening rate, limiting the accuracy of the cancer stage distribution at diagnosis. We try to overcome this issue through varying the distribution during sensitivity analysis.

Chemoprevention of breast cancer through medication, like tamoxifen or oral contraceptives, is not included in the action space, resulting in a potentially incomplete representation of a carrier's choice set. We have excluded this therapy option, as a strong risk-reducing effect of chemoprevention for all age groups and mutation types is uncertain (Duffy and Nixon 2002, King et al. 2001). The risk of breast cancer recurrence or a contralateral breast cancer (i.e., a new tumor in the opposite breast of the original tumor) is significant for mutation carriers (Graeser et al. 2009, Nilsson et al. 2014). As the state space structure does not account for recurrences or contralateral breast cancer and these states would alter a carrier's mortality, our model is limited by the accuracy of the breast cancer mortality rate. To address this limitation, we assume bilateral mastectomies in the case of a breast cancer diagnosis, which nearly eliminates the risk of contralateral cancer, and we account for distant recurrences within the overall breast cancer mortality rate.

Another limiting factor is the magnitude and duration of the impact of prophylactic surgeries on women's QOL. Empirical studies present some contradicting evidence for the impact of a BM and BSO (Harmsen et al. 2015). More importantly, women exhibit varying preferences about surgery feasibility and timing, reflecting individual differences in family planning, self-perception, and perceived risk of cancer. We do not explicitly model the decision to undergo other procedures, including breast reconstruction following a bilateral mastectomy or fertility preservation through oocyte retrieval prior to a bilateral salpingo-oophorectomy. To account for variability in these parameter values, we conduct a sensitivity analysis varying the impact of both a BM and BSO on quality of life.

6.2. Conclusions and Future Research

By developing a novel MDP model of breast and ovarian cancer and examining the structural properties of a simplified model version, we find that under the reasonable assumption that cancer risk increases with age, an optimal-control limit exists, after which surgery is always QALY maximizing. However, this analysis is limited to women who have already undergone either a BM or BSO, and it further assumes a minimal effect of a BSO on breast cancer risk.

We numerically confirm this optimal threshold policy for a BRCA mutation carrier previously diagnosed with breast cancer: she is recommended to undergo a BSO after age 46 (BRCA1) or age 48 (BRCA2). Improved breast cancer screening adherence also impacts the recommended surgery schedule. Under the optimistic assumption that *all* breast cancer tumors are diagnosed in stage I, our model recommends not performing a BM at any age, as the adverse impact on QOL is not offset by a sufficient reduction in lifetime breast cancer risk.

Our model could be extended in several ways. By combining it with an underlying cancer progression model, the individualized quality of life assumptions and cancer-specific mortality rates could become more precise. Modeling the QOL impact as a stochastic variable could capture uncertain outcomes associated with the surgeries (e.g., due to complications). With more women seeking genetic testing for cancer-causing mutations, such as BRCA1/2, decision support models such as the one we have developed can help patients make better decisions under uncertainty, to improve both the length and quality of life. Our modeling framework could provide a basis for a cost-effectiveness analysis comparing prophylactic surgery sequences against more frequent screening aimed at improving early cancer detection.

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Appendix A. Supplemental Table

Table A.1. State Space Variables and Corresponding Set of Possible Values

State variable	Value set						
Age (*age*)	20	21	22	...	85		
Prior surgery (*surg*)	None	BSO < 40	BSO = 40	...	BSO > 49	BM	BSO and BM
Breast cancer (*bc*)	None	In treatment	≤5 yrs ago	>5 yrs ago			
Breast cancer tumor stage (*bcts*)	None	I	II	III	IV		
Breast cancer tumor subtype (*bcsu*)	None	Luminal A	Luminal B	HER2	Triple negative		
Ovarian cancer (*oc*)	None	In treatment	Post-treatment				
Ovarian cancer tumor stage (*octs*)	None	I	II	III	IV		
Death (*de*)	Alive	Metastatic cancer death	Other death				

Appendix B. Structural Properties

B.1. Limited Problem Scope: Prior Breast Cancer

Following breast cancer diagnosis and treatment, the relevant action set A is reduced to $\hat{A} = \{W, BSO\}$, with a BSO as the only remaining surgery option. The state space is reduced to a one-dimensional vector $\hat{S} = \{x^{20}, x^{21}, \ldots, x^{85}, x^{bso}, x^{oc}, x^{death}\}$. The first set of states, $x^{20}, x^{21}, \ldots, x^{85}$, represent the carrier's age, each with an age-specific ovarian cancer risk. For each of these states, it is assumed that a BM has already been performed as part of breast cancer treatment. We combine the state variables *oc* and *octs* into a single state x^{oc}, which indicates the diagnosis of ovarian cancer. The state x^{bso} indicates that prophylactic BSO surgery has been performed as the result of taking action BSO. Finally, x^{death} indicates the death of the carrier through metastatic cancer or other causes, with immediate reward $r_t(x^{death}, \cdot) = 0$. If a BSO surgery occurs, the action set is reduced to $\hat{A}(x^{bso}) = \{W\}$, and the corresponding reward $r_t(x^{bso}, W)$ is reduced by the impact of the surgery on QOL. If ovarian cancer occurs, the reward $r_t(x^{oc}, \cdot)$ is reduced by the impact of the cancer itself.

In the model's final decision epoch, T, we assume that the immediate reward of performing a BSO in T, or waiting, both equal the discounted remaining QALYs of a healthy mutation carrier at T. To justify this, we allow T to be sufficiently large, such that remaining discounted QALYs are small (i.e., an 85 year old woman is more likely to die from other causes than from ovarian cancer, consistent with the clinical observation that most elderly patients who are diagnosed with ovarian cancer do not receive aggressive treatment options; Lambrou and Bristow 2003). We therefore obtain the following boundary conditions:

$$r_T(s_T, BSO) = r_T(s_T, W) = v_T(s_T), \quad \forall\, s_T \in \{x^{20}, x^{21}, \ldots, x^{85}\}. \tag{B.1}$$

The terminal reward after undergoing a BSO surgery accounts for reduced mortality through cancer risk reduction and the QOL impact of the BSO:

$$r_T(x^{bso}, W) = v_T(x^{bso}). \tag{B.2}$$

Similarly, the terminal reward after a cancer diagnosis equals discounted remaining QALYs of a mutation carrier diagnosed with cancer who is still alive at age T:

$$r_T(x^{oc}, W) = v_T(x^{oc}). \tag{B.3}$$

To show structural properties for this limited problem scope, we first make the following assumptions:

Assumption 1. *The probability of developing ovarian cancer $p_t(x^{oc} \mid s_t, W)$ without a preventive BSO is nondecreasing in s_t, $\forall\, s_t \in \{x^{20}, x^{21}, \ldots, x^{85}\}$.*

A meta-analysis of multiple clinical studies supports Assumption 1 that the annual risk of developing ovarian cancer remains constant or increases as a carrier ages (Chen and Parmigiani 2007).

Assumption 2. *The immediate reward $r_t(s_t, W)$ is nonincreasing in s_t, $\forall\, s_t \in \hat{S}$ and in t.*

Assumption 2 implies that a carrier's quality of life remains constant or decreases as she ages, $s_t \in \{x^{20}, x^{21}, \ldots, x^{85}\}$ (Asakawa et al. 2012); undergoes a BSO, $s_t \in \{x^{bso}\}$ (Grann et al. 2010); develops ovarian cancer, $s_t \in \{x^{oc}\}$ (Grann et al. 2010, 1999a); or dies, $s_t \in \{x^{death}\}$.

Assumption 3. *The function $v_t(s_t, BSO)$ is nonincreasing in s_t, $\forall\, s_t \in \{x^{20}, x^{21}, \ldots, x^{85}\}$, and in t.*

Assumption 3 requires that a carrier's expected remaining QALYs following a BSO remains constant or decreases as she ages, which is reasonable if quality of life decreases as women age (Asakawa et al. 2012). Any decrement in QOL of a BSO after the onset of natural menopause is offset by the decrease in life expectancy as age increases.

Assumption 4. *The functions $v_t(x^{bso}, \cdot)$ and $v_t(x^{oc}, \cdot)$ are nonincreasing in t.*

Assumption 4 implies that a carrier's expected remaining QALYs after undergoing a BSO or developing ovarian cancer remains constant or decreases as she ages (Asakawa et al. 2012).

Assumption 5. $v_t(s_t, BSO) \geq v_t(x^{oc}, BSO)$, $\forall\, s_t \in \{x^{20}, x^{21}, \ldots, x^{85}\}$.

Assumption 5 requires that the expected remaining QALYs following a BSO are at least as great as the expected remaining QALYs after ovarian cancer (Grann et al. 1999a, 2010), which is clinically sound as ovarian cancer treatment typically includes a BSO in addition to other treatment modalities such as chemotherapy, radiation, and endocrine therapy, all of which substantially reduce quality of life (Tengs and Wallace 2000). A carrier diagnosed with ovarian cancer also has lower overall survival than a woman without cancer because of metastatic recurrence risk (Bolton et al. 2012).

Assumption 6. *The transition probabilities given action W satisfy the following*:

$$p_t(x^{oc} \mid s_t, W) \leq p_{t+1}(x^{oc} \mid s_t, W) \quad \forall\, s_t \in \{x^{20}, x^{21}, \ldots, x^{85}\},$$
$$p_t(x^{death} \mid s_t, W) \leq p_{t+1}(x^{death} \mid s_t, W) \quad \forall\, s_t \in \{x^{20}, x^{21}, \ldots, x^{85}\}.$$

Assumption 6 means that ovarian cancer risk is nondecreasing in t; as a carrier ages, she is more likely to transition to a worse health state (i.e., ovarian cancer or death) if she chooses to not undergo a BSO. A large meta-analysis of 10 studies estimates that the risk of ovarian cancer increases with each decade from age 30 to 70 years, in both BRCA1 and BRCA2 mutation carriers (Chen and Parmigiani 2007).

Definition 1 (Barlow and Proschan 1965)**.** A Markov chain's transition probability matrix, P, with one-step transition probabilities $p(j \mid i)$ has the increasing failure rate (IFR) property if its rows are in increasing stochastic order; that is,

$$q(i) = \sum_{j=k}^{x^{death}} p(j \mid i) \tag{B.4}$$

is nondecreasing in i, $\forall\, k \in \{x^{20}, x^{21}, \ldots, x^{death}\}$.

The above definition means that for the underlying Markov chain of the MDP, as a carrier progresses into states with a higher cancer risk, her risk of progressing to states with an even higher risk of death also increases.

To show the existence of an optimal control limit for performing a BSO, we first show the monotonicity of $v_t(s_t)$ in s_t and t. All proofs are given in Section B.3.

Proposition 1. *If the transition probability matrix for action W is IFR for all $t = 1, 2, \ldots, T$, then $v_t(s_t)$ is nonincreasing in s_t, for $s_t = x^{20}, x^{21}, \ldots, x^{85}$, and $t = 1, 2, \ldots, T-1$.*

In Proposition 1, we show that $v_t(s_t)$ is nonincreasing in s_t, implying that a carrier's expected QALYs do not increase with her age and cancer risk, respectively. As a consequence, the following relationship also holds:

Lemma 1. *If Assumption 6 holds for $t = 1, 2, \ldots, T-1$, then for any $f(i)$ nonincreasing in i, the following holds*:

$$\sum_{s'_t \in \hat{S}} p_t(s'_t \mid i) f(s'_t) \geq \sum_{s'_t \in \hat{S}} p_{t+1}(s'_t \mid i) f(s'_t). \tag{B.5}$$

Lemma 1 indicates that $v_t(s_t)$ is nonincreasing in t; in other words, a carrier's expected remaining QALYs do not increase as she ages.

Proposition 2. *The optimal value function, $v_t(s_t)$, is nonincreasing in t for all $s_t \in \hat{S}$.*

Lemma 2. *Let $\mathbf{P} = [p_t(j \mid i)]$ be an IFR transition probability matrix for $i, j = 1, 2, \ldots, N$, such that $\sum_{k=i+1}^{k^*} p_t(k \mid i+1) \geq \sum_{k=i+1}^{k^*} p_t(k \mid i)$ for $i < k^* \leq N$ and $t = 1, 2, \ldots, T-1$. If $f(i)$ is a nonincreasing function in i, then the following holds*:

$$\sum_{k=1}^{i} \{p_t(k \mid i) - p_t(k \mid i+1)\} f(k) \geq \sum_{k=1}^{i} \{p_t(k \mid i) - p_t(k \mid i+1)\} f(i), \tag{B.6}$$

$$\sum_{k'=i+1}^{k^*} \{p_t(k' \mid i) - p_t(k' \mid i+1)\} f(k') \geq \sum_{k'=i+1}^{k^*} \{p_t(k' \mid i) - p(k' \mid i+1)\} f(i+1). \tag{B.7}$$

Using Lemma 2, we can show that an optimal control policy exists.

Theorem 1. *If the transition probability matrix P_t for action W is IFR and satisfies the two conditions*

$$\frac{v_t(s_t, BSO) - v_t(s_t+1, BSO)}{\gamma v_{t+1}(s_t+1, BSO)} \leq p_t(x^{death} \mid s_t+1, W) - p_t(x^{death} \mid s_t, W), \tag{B.8}$$

$$\sum_{s'=s_t+1}^{x^{death}} p_t(s' \mid s_t+1, W) \geq \sum_{s'=s_t+1}^{x^{death}} p_t(s' \mid s_t, W), \tag{B.9}$$

for all $s_t \in \{x^{20}, x^{21}, \ldots, x^{85}\}$ and $t = 1, 2, \ldots, T-1$, then there exists an optimal control threshold state $\bar{s}_t \in \{x^{20}, x^{21}, \ldots, x^{85}\}$ for $t = 1, 2, \ldots, T-1$ such that

$$a^*(s_t) = \begin{cases} W & \text{if } s_t < \bar{s}_t, \\ BSO & \text{if } s_t \geq \bar{s}_t. \end{cases} \tag{B.10}$$

Inequality (B.8) denotes that as a carrier's age increases, the *decrease* in QOL due to a BSO is less than the *increase* in mortality risk by waiting one additional period. Inequality

(B.9) requires that the probability of moving to a higher risk state or death increases with age.

B.2. Limited Problem Scope: Prior Ovarian Cancer

An equivalent structural property can be derived for a BRCA mutation carrier's decision to undergo prophylactic BM following an ovarian cancer diagnosis and treatment. The revised state space is $\hat{S} = \{x^{20}, x^{21}, \ldots, x^{85}, x^{bm}, x^{bc}, x^{death}\}$, and the revised action set is $\hat{A} = \{W, BM\}$. Following a similar set of structural analyses as before, we obtain a similar theorem:

Theorem 2. *If the transition probability matrix P_t for action W is IFR for and satisfies the conditions*

$$\frac{v_t(s_t, BM) - v_t(s_t + 1, BM)}{\gamma v_{t+1}(s_t + 1, BM)} \leq p_t(x^{death} \mid s_t + 1, W) - p_t(x^{death} \mid s_t, W), \tag{B.11}$$

$$\sum_{s'=s_t+1}^{x^{death}} p_t(s' \mid s_t + 1, W) \geq \sum_{s'=s_t+1}^{x^{death}} p_t(s' \mid s_t, W), \tag{B.12}$$

for all $s_t \in \{x^{20}, x^{21}, \ldots, x^{85}\}$ and $t = 1, 2, \ldots, T-1$, then there exists an optimal control threshold state $\bar{s}_t \in \{x^{20}, x^{21}, \ldots, x^{85}\}$ for $t = 1, 2, \ldots, T-1$ such that

$$a^*(s_t) = \begin{cases} W & \text{if } s_t < \bar{s}_t, \\ BM & \text{if } s_t \geq \bar{s}_t. \end{cases} \tag{B.13}$$

In Section 5, we provide numerical results for Theorems 1 and 2.

B.3. Proofs

Proof of Proposition 1. The proof of Proposition 1 is similar to the proof of Proposition 4.7.3 in Puterman (2014) and therefore omitted here. □

Proof of Lemma 1. The sum over a row in the transition probability matrix requires the relation $\sum_{s'=x^{20}}^{x^{death}} p_t(s' \mid i) = \sum_{s'=x^{20}}^{x^{death}} p_{t+1}(s' \mid i) = 1$. Let

$$E = \sum_{s'=x^{20}}^{x^{death}} p_{t+1}(s' \mid i) - \sum_{s'=x^{20}}^{x^{death}} p_t(s' \mid i). \tag{B.14}$$

If $f(i)$ is nonincreasing in i, then

$$\begin{aligned} &\left\{\sum_{s'=x^{20}}^{x^{death}} p_{t+1}(s' \mid i) - \sum_{s'=x^{20}}^{x^{death}} p_t(s' \mid i)\right\} f(x^{20}) \\ &\quad \geq [p_{t+1}(x^{20} \mid i) - p_t(x^{20} \mid i)] f(x^{20}) \\ &\qquad + \left\{\sum_{s'=x^{21}}^{x^{death}} p_{t+1}(s' \mid i) - \sum_{s'=x^{21}}^{x^{death}} p_t(s' \mid i)\right\} f(x^{21}) \\ &\quad \geq \left\{\sum_{s'=x^{20}}^{x^{21}} p_{t+1}(s' \mid i) - \sum_{s'=x^{20}}^{x^{21}} p_t(s' \mid i)\right\} f(s') \\ &\qquad + \left\{\sum_{s'=x^{22}}^{x^{death}} p_{t+1}(s' \mid i) - \sum_{s'=x^{22}}^{x^{death}} p_t(s' \mid i)\right\} f(x^{22}). \end{aligned} \tag{B.15}$$

It follows that

$$E \geq \sum_{s'=x^{20}}^{x^{death}} p_{t+1}(s' \mid i) f(s') - \sum_{s'=x^{20}}^{x^{death}} p_t(s' \mid i) f(s'), \tag{B.16}$$

which leads to $\sum_{s' \in \hat{S}} p_t(s' \mid i) f(s') \geq \sum_{s' \in \hat{S}} p_{t+1}(s' \mid i) f(s')$. □

Proof of Proposition 2. We use backward induction to prove this Proposition. For $t = T-1$,

$$\begin{aligned} v_{T-1}(s_{T-1}) &\geq r_{T-1}(s_{T-1}, BSO) \\ &\geq r_T(s_T, BSO) \qquad \text{(B.17)} \\ &= v_T(s_T). \qquad \text{(B.18)} \end{aligned}$$

Assumptions 2 and 3 can be used to deduce (B.17), and the boundary condition of given in Equation (B.1) leads to (B.18). It follows that $v_{T-1}(s_{T-1}) \geq v_T(s_T)$, which is a sufficient proof for the base case. The proposition is assumed to hold as well for $t = t_0 \; \forall \, s_t \in \hat{S}$. That the theorem holds for $t = t_0 - 1$ is proven through

$$\begin{aligned} &v_{t_0-1}(s_t) \\ &= \max\Big\{r_{t_0-1}(s_{t_0-1}, BSO) + \gamma \sum_{s' \in \hat{S}} p_{t_0-1}(s' \mid s_{t_0-1}, BSO) v_{t_0}(x'), \\ &\qquad r_{t_0-1}(s_{t_0-1}, W) + \gamma \sum_{s' \in \hat{S}} p_{t_0-1}(s' \mid s_{t_0-1}, W) v_{t_0}(s')\Big\} \\ &\geq \max\Big\{r_{t_0}(s_{t_0}, BSO) + \gamma \sum_{s' \in \hat{S}} p_{t_0}(s' \mid s_{t_0}, BSO) v_{t_0}(s'), \\ &\qquad r_{t_0}(s_{t_0}, W) + \gamma \sum_{s' \in \hat{S}} p_{t_0}(s' \mid s_{t_0}, W) v_{t_0}(s')\Big\} \qquad \text{(B.19)} \\ &\geq \max\Big\{r_{t_0}(s_{t_0}, BSO) + \gamma \sum_{s' \in \hat{S}} p_{t_0}(s' \mid s_{t_0}, BSO) v_{t_0+1}(s') \\ &\qquad r_{t_0}(s_{t_0}, W) + \gamma \sum_{s' \in \hat{S}} p_{t_0}(s' \mid s_{t_0}, W) v_{t_0+1}(s')\Big\} \qquad \text{(B.20)} \\ &= v_{t_0}(s_{t_0}), \qquad \text{(B.21)} \end{aligned}$$

where (B.19) follows from Assumptions 1–3 and Lemma 1. The induction hypothesis $v_{t_0}(s_t) \geq v_{t_0+1}(s_t)$ leads to (B.20). The proposition therefore holds for all $t = 1, 2, \ldots, T-1$. □

Proof of Lemma 2. The following proof of Lemma 2 is given for the infinite case in Alagoz et al. (2004). To prove Equation (B.6), we repeat that the IFR assumption implies that $\sum_{j=1}^{k} p_t(j \mid i) \geq \sum_{j=1}^{k} p_t(j \mid i+1)$ for any $k \in \hat{S}$. Let

$$\begin{aligned} &\sum_{k=1}^{i} \{p_t(k \mid i) - p_t(k \; i+1)\} f(k) \\ &= \{p_t(x^{21} \mid i) - p_t(x^{21} \mid i+1)\} f(x^{21}) \\ &\quad + \sum_{k=x^{22}}^{i} \{p_t(k \mid i) - p_t(k \mid i+1)\} f(k) \\ &\geq \{p_t(x^{21} \mid i) - p_t(x^{21} \mid i+1)\} f(x^{22}) \end{aligned}$$

$$+\sum_{k=x^{22}}^{i}\{p_t(k\mid i)-p_t(k\mid i+1)\}f(k) \tag{B.22}$$

$$=\{p_t(x^{21}\mid i)+p_t(x^{22}\mid i)-p_t(x^{21}\mid i+1)-p_t(x^{22}\mid i+1)\}f(x^{22})$$
$$+\sum_{k=x^{23}}^{i}\{p_t(k\mid i)-p_t(l\mid i+1)\}f(k)$$
$$\geq\{p_t(x^{21}\mid i)+p_t(x^{22}\mid i)-p_t(x^{21}\mid i+1)-p_t(x^{22}\mid i+x^{22})\}f(x^{23})$$
$$+\sum_{k=x^{23}}^{i}\{p_t(k\mid i)-p_t(k\mid i+1)\}f(k), \tag{B.23}$$

with (B.22) following from $p_t(x^{21}\mid i)\geq p_t(x^{21}\mid i+1)$ and $f(x^{21})\geq f(x^{22})$. Inequality (B.23) holds as $p_t(x^{21}\mid i)+p_t(x^{22}\mid i)\geq p_t(x^{21}\mid i+1)$ and $v(x^{21})\geq v(x^{22})$. The complete proof follows from the application of the same procedure to the remaining states $x^{23},\ldots,x^{death}$. Equation (B.7) requires a similar proof, which is omitted here. □

Proof of Theorem 1. The following inequalities hold if $a^*(s_t)$ exists:

$$v_t(\bar{s}_t,BSO)\geq r_t(\bar{s}_t,W)+\gamma\sum_{s'\in\hat{S}}p_t(s'\mid\bar{s}_t,W)v_{t+1}(s'), \tag{B.24}$$

$$v_t(\bar{s}_t+1,BSO)\geq r_t(\bar{s}_t+1,W)+\gamma\sum_{s'\in\hat{S}}p_t(s'\mid\bar{s}_t+1,W)v_{t+1}(s'). \tag{B.25}$$

Assume $a^*(s_t)=BSO$ for $s_t=\bar{s}_t$ and $a^*(s_t+1)=W$ only for $s_t=\bar{s}_t+1$, and $t=0,1,\ldots,T-1$. It follows that

$$v_t(\bar{s}_t,BSO)\geq r_t(\bar{s}_t,W)+\gamma\sum_{s'\in\hat{S}}p_t(s'\mid\bar{s}_t,W)v_{t+1}(s'), \tag{B.26}$$

$$v_t(\bar{s}_t,BSO)<r_t^*(\bar{s}_t+1,W)+\gamma\sum_{s'\in\hat{S}}p_t(s'\mid\bar{s}_t+1,W)v_{t+1}(s'), \tag{B.27}$$

$$v_t(\bar{s}_t,BSO)-v(\bar{s}_t+1,BSO)>r_t(\bar{s}_t,W)-r_t(\bar{s}_t+1,W)$$
$$+\gamma\sum_{s'\in\hat{S}}\{p_t(s'\mid\bar{s}_t,W)-p_t(s'\mid\bar{s}_t+1,W)\}v_{t+1}(s') \tag{B.28}$$

$$\geq\gamma\sum_{s'\in\hat{S}}\{p_t(s'\mid\bar{s}_t,W)-p_t(s'\mid\bar{s}_t+1,W)\}v_{t+1}(s') \tag{B.29}$$

$$=\gamma\sum_{s'=0}^{\bar{s}_t}\{p_t(s'\mid\bar{s}_t,W)-p_t(s'\mid\bar{s}_t+1,W)\}v_{t+1}(s')$$
$$+\gamma\sum_{s''=\bar{s}_t+1}^{x^{85}}\{p_t(s''\mid\bar{s}_t,W)-p_t(s''\mid\bar{s}_t+1,W)\}v_{t+1}(s'') \tag{B.30}$$

$$\geq\gamma\sum_{s'=0}^{s_t*}\{p_t(s'\mid s_t*,W)-p_t(s'\mid\bar{s}_t+1,W)\}v_{t+1}(\bar{s}_t)$$
$$+\gamma\sum_{s''=\bar{s}_t+1}^{x^{85}}\{p_t(s''\mid\bar{s}_t,W)-p_t(s''\mid\bar{s}_t+1,W)\}v_{t+1}(\bar{s}_t+1) \tag{B.31}$$

$$\geq\gamma\sum_{s'=0}^{s_t*}\{p_t(s'\mid\bar{s}_t,W)-p_t(s'\mid\bar{s}_t+1,W)\}v_{t+1}(\bar{s}_t+1)$$
$$+\gamma\sum_{s''=\bar{s}_t+1}^{x^{85}}\{p_t(s''\mid\bar{s}_t,W)-p_t(s''\mid\bar{s}_t+1,W)\}v_{t+1}(\bar{s}_t+1) \tag{B.32}$$

$$=\gamma\sum_{s'=0}^{x^{85}}\{p_t(s'\mid\bar{s}_t,W)-p_t(s'\mid\bar{s}_t+1,W)\}v_{t+1}(\bar{s}_t+1) \tag{B.33}$$

$$\geq\gamma\sum_{s'=0}^{x^{85}}\{p_t(s'\mid\bar{s}_t,W)-p_t(s'\mid\bar{s}_t+1,W)\}v_{t+1}(\bar{s}_t+1,BSO) \tag{B.34}$$

$$=\gamma\{p_t(x^{death}\mid\bar{s}_t+1,W)-p_t(x^{death}\mid\bar{s}_t,W)\}r_{t+1}(\bar{s}_t+1,BSO). \tag{B.35}$$

Inequality (B.29) follows from Assumption 1 as well as $p_t(j\mid s,W)=0$ for $j\in\{x^{bso}\}$ and $s\in\hat{S}\backslash x^{bso}$. Inequality (B.31) follows from Proposition 1 and Lemma 2. Being IFR, $\mathbf{P}_t^W$ has the IFR property, which implies that $\sum_{s'=s_t+1}^{x^{death}}p_t(s'\mid s_t,W)\leq\sum_{s'=s_t+1}^{x^{death}}p_t(s'\mid s_t+1,W)$ and $\sum_{s'=0}^{s_t}p_t(s'\mid s_t,W)\geq\sum_{s'=s_t}^{s_t}p_t(s'\mid s_t+1,W)$. By using Proposition 1 to state that $v_{t+1}(s_t)\geq v_{t+1}(s_t+1)$, $v_{t+1}(s_t)$ in Equation (B.31) can be replaced by $v_{t+1}(s_t+1)$ in Equation (B.32). With $\mathbf{P}_t^W$ having the IFR property and $v_{t+1}(s_t+1)\geq r_{t+1}(s_t+1,BSO)$, we can conclude inequality (B.34). Equation (B.35) can therefore be replaced by

$$\frac{v_t(\bar{s}_t,BSO)-v_t(\bar{s}_t+1,BSO)}{v_{t+1}(\bar{s}_t+1,BSO)}>\gamma\{p_t(x^{death}\mid\bar{s}_t+1,W)-p_t(x^{death}\mid\bar{s}_t,W)\}, \tag{B.36}$$

which contradicts Equation (1), from which the proof follows. □

Proof of Theorem 2. The proof is similar to that of Theorem 1 with *BSO* replaced by *BM*. □

Appendix C. Data Format Conversion

This section describes the formulas used to convert the data collected from different clinical studies into a form that is usable in the MDP's transition probability matrices.

C.1. Cancer Risk

Chen and Parmigiani (2007) provide the conditional probability of developing breast and ovarian cancer in 10-year intervals (e.g., the conditional probability of a 40-year-old woman without cancer developing breast cancer by age 50). We estimate piecewise-constant rates of developing breast or ovarian cancer, which increase as women age. We chose this structure—as opposed to interpolating cancer risk—so that our cumulative cancer probabilities could be readily compared with the medical literature. We first calculate the constant rate, r, of an event to achieve a probability, p_{10}, of the event occurring in 10 years:

$$r=-\frac{\ln(1-p_t)}{t}. \tag{C.1}$$

Using the constant rate, r, we then calculate the one-year probability, p_1, according to

$$p_t=1-e^{-rt}. \tag{C.2}$$

C.2. Risk Reduction Given as Odds Ratio

The cancer risk reduction following prophylactic surgery is given as an odds ratio (OR), defined as

$$OR = \frac{q/(1-q)}{p/(1-p)}, \tag{C.3}$$

where p is the baseline probability of a specific cancer and q is the revised probability after surgery (Eisen et al. 2005). Therefore, the probability of cancer after prophylactic surgery is

$$q = \frac{p \times OR}{1 - p + p \times OR}. \tag{C.4}$$

Our calculated values of the postsurgery probability of cancer are generally consistent with those of Grant (2014).

C.3. Risk Reduction Given as Hazard Ratio

A hazard ratio (HR) is also given in some studies, defined as the ratio of the *rates* of developing a specific cancer before and after prophylactic surgery (Rebbeck et al. 2004, 2009). We convert a probability p of being diagnosed with cancer in t years to a constant hazard rate r using the formula

$$r = -\frac{\ln(1-p)}{t} \tag{C.5}$$

The revised rate is then adjusted by multiplying r by the HR.

Appendix D. Model Verification and Validation

To ensure that the model described in Section 3 matches reality in the intended way, we follow model verification and validation steps proposed by Gass (1984).

D.1. Model Verification

Model verification aims to ensure that the model runs as intended, which in our case means that the written software matches the mathematical expressions given in the model description. The methods used during the model development process are common in software development projects:

- *Modular coding*. We begin by coding a very simple MDP containing only one variable and solve for the optimal policy using example parameters. Once accurate performance has been assured, we add the next variable and test the model behavior with an extended set of example parameters. This iterative procedure is repeated until the full MDP is constructed.
- *Documentation*. To document the content of the algorithm and to make it easily interpretable for people not involved in the research project, we comment on the non-self-explanatory lines of code while writing the algorithms.
- *Model verification*. To ensure accuracy of the full model, we perform sensitivity analysis by varying specific parameter values and resolving for the optimal policy. We also conduct simulations of the underlying MDP and carefully examine whether the model behaves as expected.

D.2. Model Validation

According to Gass (1984), model validation "tests the agreement between the behavior of the model and the real world system being modeled." We apply validation techniques defined by Gass (1984) as well as Sargent (2013) to our model:

- *Comparison to other models*. We compare the outputs of our model with existing publications in the research area (Abdollahian and Das 2015, Grann et al. 1998, van Roosmalen et al. 2002, Kurian et al. 2014). Although our optimal policy does not exactly match the prior work of Abdollahian and Das (2015), our projections of lifetime cancer risk are generally consistent with these other studies.
- *Data validity*. While most of our parameter values have been empirically estimated during clinical studies, we use only recent studies with a sufficient population size (see also Section 5.1).
- *Face validity*. The input parameters and assumptions were discussed with clinical experts in the field of breast and ovarian cancer at the UCLA David Geffen School of Medicine and the University Medical Center Hamburg-Eppendorf in Germany.
- *Extreme condition tests*. We test the model output behavior through setting the input parameters to extreme levels, e.g., assuming a QALY impact of prophylactic surgeries of 0 or 1 or setting the risk of one cancer to 0 or 1. In particular, we compare our model's projected life expectancy in women, assuming no additional breast or ovarian cancer risk due to a BRCA mutation, to published life expectancy estimates from the U.S. Centers for Disease Control and Prevention (2014; Table D.1).
- *Logical/Mathematical validity*. The model structure is documented for validation in Section 3 and analyzed in Appendix B. Markov decision process models have been applied numerous times to similar research questions (see Section 2).
- *Sensitivity analysis*. We run a wide set of sensitivity analyses to test the robustness of our approach under different parameter assumptions (see Section 5).

Table D.1. Comparison Between Model Calculations of Life Expectancy and Published Values for Non-BRCA Mutatation Carriers

Current age (years)	Model projection (years)	CDC estimate (years)	Error (%)
20	78.8	79.6	0.99
40	79.9	80.7	1.04
60	82.1	83.2	1.31

Appendix E. Additional Sensitivity Analyses

E.1. Improved Breast Cancer Screening or Treatment

Figure E.1. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That All Breast Cancers Are Detected in Stage I Due to Perfect Screening Conditions

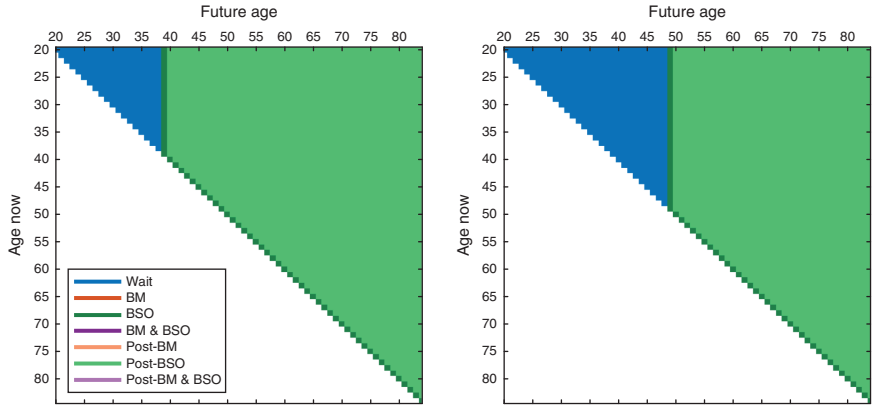
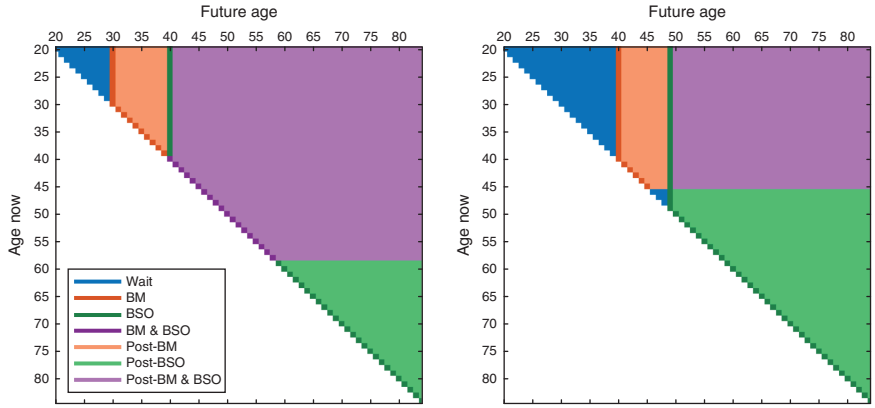
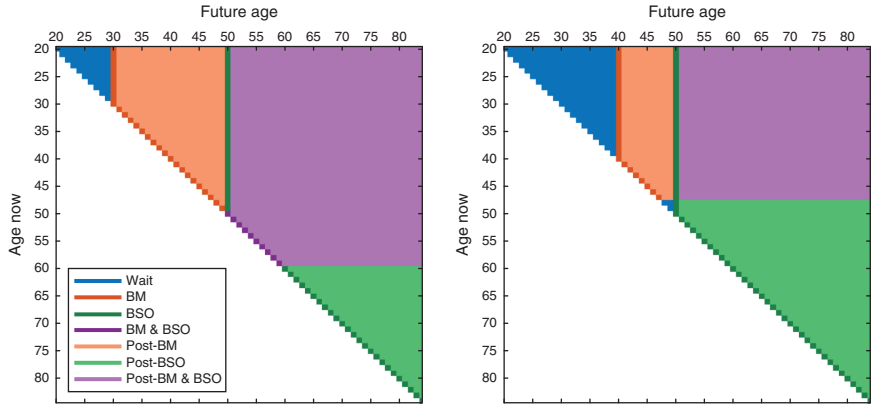


Figure E.2. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers If Triple Negative Breast Cancer Has Similar Mortality as Luminal A Due to Treatment Advances



E.2. Fertility Considerations

Figure E.3. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Who Prefer to Not Undergo a Prophylactic BSO Before Age 50



E.3. Constrained Surgery Options

Figure E.4. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Who Prefer to Not Undergo Any Prophylactic Surgery Before Age 50

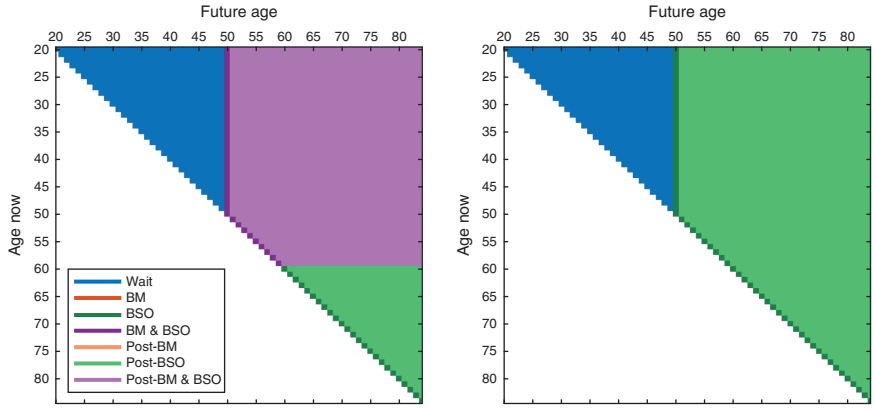
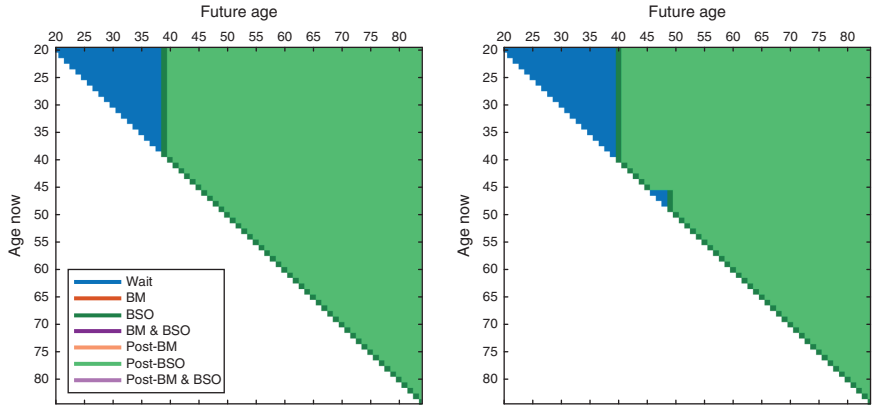


Figure E.5. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Who Prefer to Never Undergo a Prophylactic BM



E.4. Breast Cancer Risk Reduction Following Bilateral Mastectomy

Figure E.6. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That the Breast Cancer Risk Reduction After BM Is the Upper 95% CI Limit (Table 2)

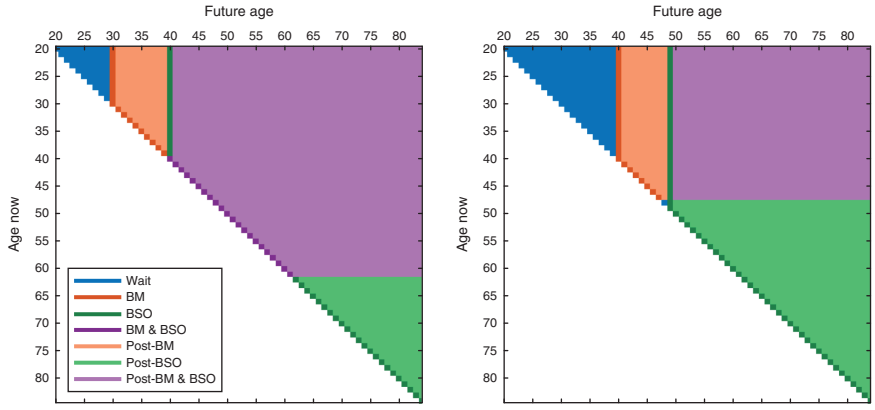
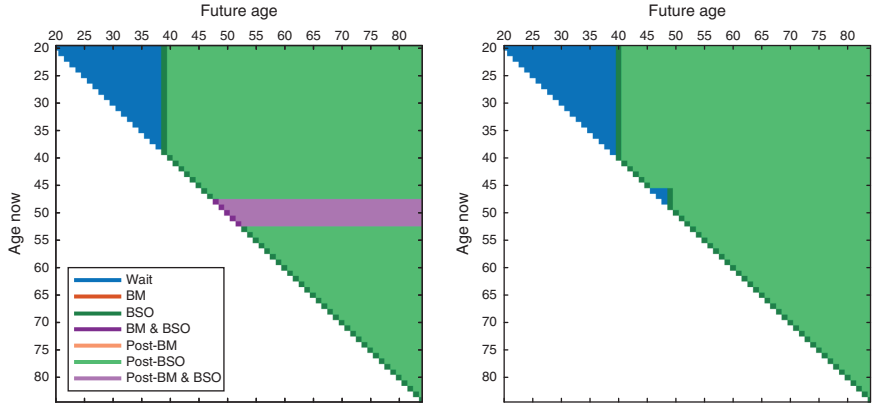


Figure E.7. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That the Breast Cancer Risk Reduction After BM Is the Lower 95% CI Limit (Table 2)



E.5. Breast Cancer Risk Reduction Following Bilateral Salpingo-Oophorectomy

Figure E.8. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That the Breast Cancer Risk Reduction After BSO Is the Upper 95% CI Limit (Table 2)

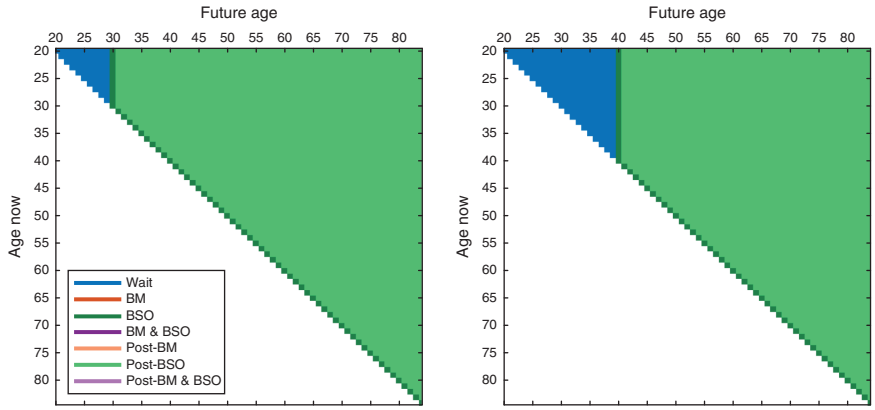
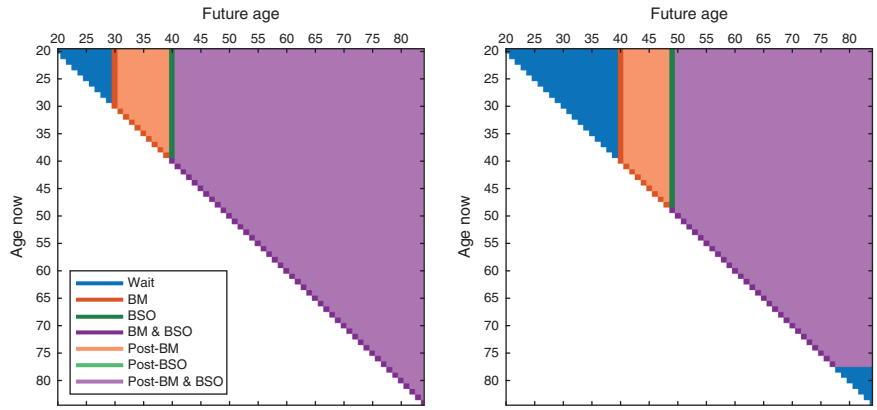


Figure E.9. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That the Breast Cancer Risk Reduction After BSO Is the Lower 95% CI Limit (Table 2)



E.6. Ovarian Cancer Risk Reduction Following Bilateral Salpingo-Oophorectomy

Figure E.10. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That the Ovarian Cancer Risk Reduction After BSO Is the Upper 95% CI Limit (Table 2)

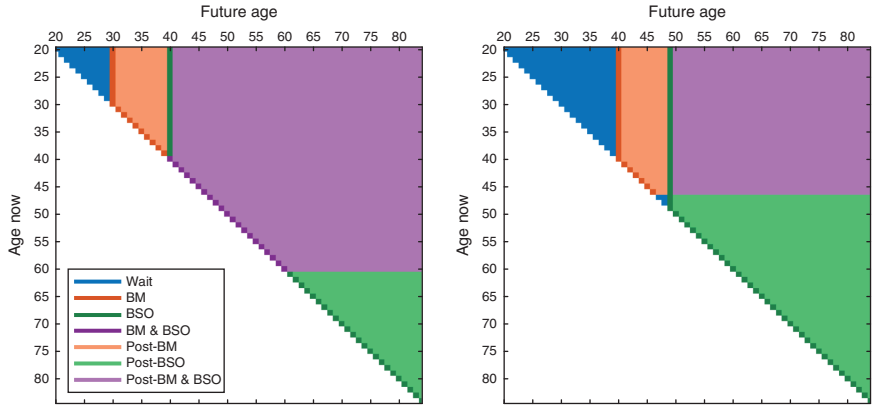
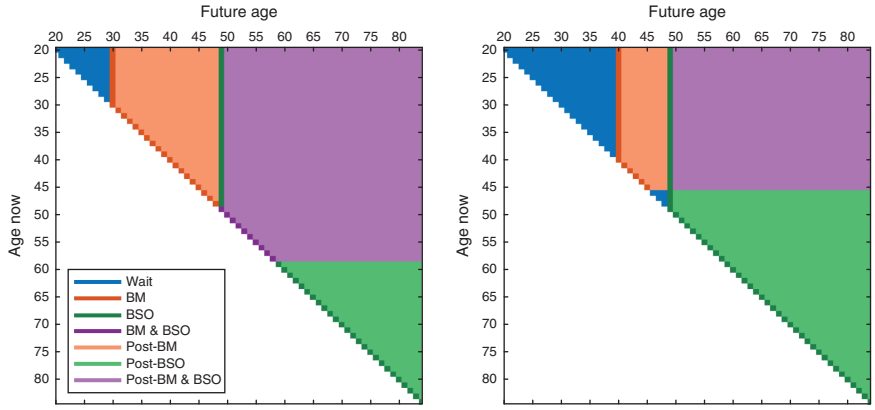


Figure E.11. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That the Ovarian Cancer Risk Reduction After BSO Is the Lower 95% CI Limit (Table 2)



E.7. Breast Cancer Mortality Rates

Figure E.12. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That Breast Cancer Mortality Rates Are Increased by 20% Across All Subtypes and Stages

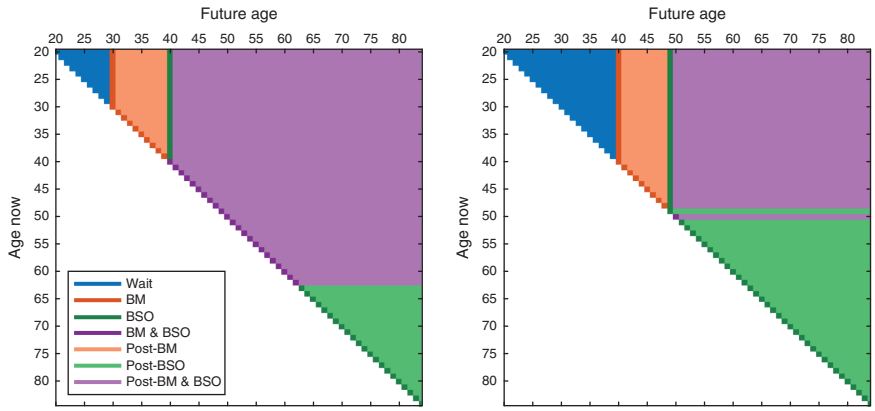
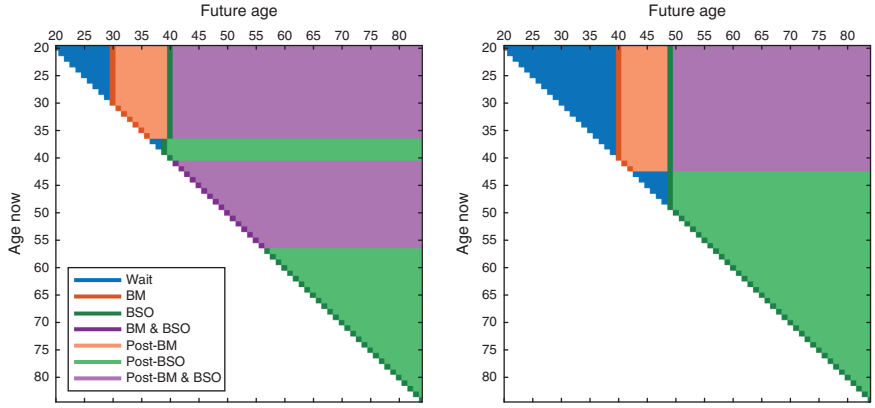


Figure E.13. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That Breast Cancer Mortality Rates Are Reduced by 20% Across All Subtypes and Stages



E.8. Ovarian Cancer Mortality Rates

Figure E.14. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That Ovarian Cancer Mortality Rates Are Increased by 20% Across All Subtypes and Stages

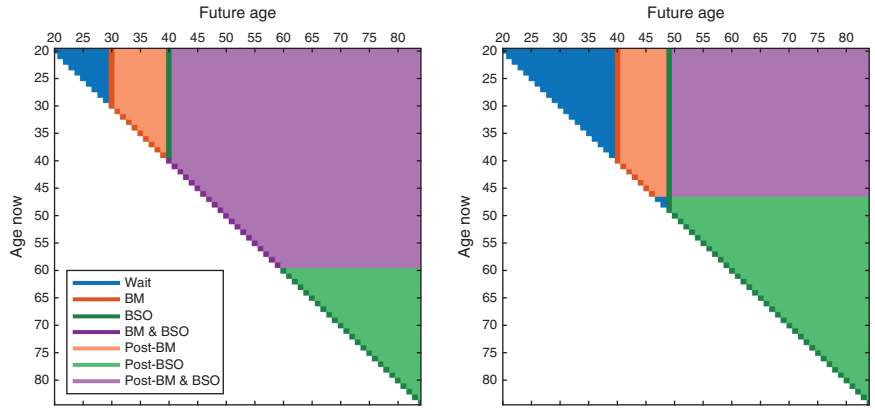
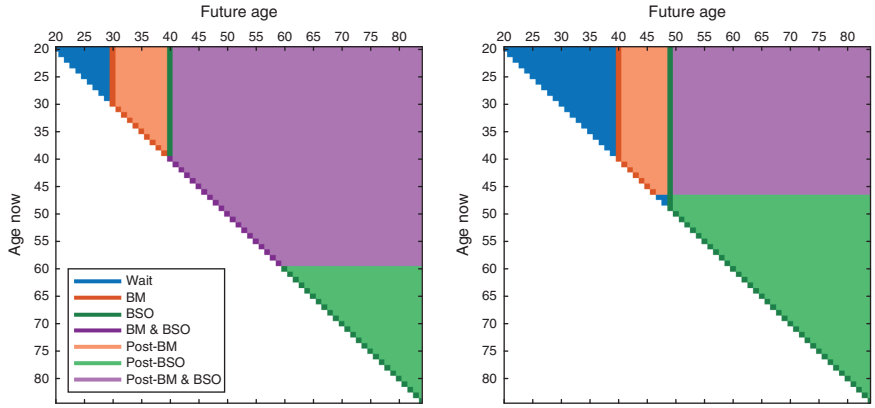


Figure E.15. QALY-Maximizing Surgery Sequence for BRCA1 (Left) and BRCA2 (Right) Carriers Assuming That Ovarian Cancer Mortality Rates Are Reduced by 20% Across All Subtypes and Stages



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