Research Article

Cancer Epidemiology, Biomarkers & Prevention

A Simulation Model to Predict the Impact of Prophylactic Surgery and Screening on the Life Expectancy of *BRCA1* and *BRCA2* Mutation Carriers

Bronislava M. Sigal[1], Diego F. Munoz[1], Allison W. Kurian[2,3], and Sylvia K. Plevritis[1]

Abstract

Background: Women with inherited mutations in the *BRCA1* or *BRCA2* (*BRCA1/2*) genes are recommended to undergo a number of intensive cancer risk-reducing strategies, including prophylactic mastectomy, prophylactic oophorectomy, and screening. We estimate the impact of different risk-reducing options at various ages on life expectancy.

Methods: We apply our previously developed Monte Carlo simulation model of screening and prophylactic surgery in *BRCA1/2* mutation carriers. Here, we present the mathematical formulation to compute age-specific breast cancer incidence in the absence of prophylactic oophorectomy, which is an input to the simulation model, and provide sensitivity analysis on related model parameters.

Results: The greatest gains in life expectancy result from conducting prophylactic mastectomy and prophylactic oophorectomy immediately after *BRCA1/2* mutation testing; these gains vary with age at testing, from 6.8 to 10.3 years for *BRCA1* and 3.4 to 4.4 years for *BRCA2* mutation carriers. Life expectancy gains from delaying prophylactic surgery by 5 to 10 years range from 1 to 9.9 years for *BRCA1* and 0.5 to 4.2 years for *BRCA2* mutation carriers. Adding annual breast screening provides gains of 2.0 to 9.9 years for *BRCA1* and 1.5 to 4.3 years for *BRCA2*. Results were most sensitive to variations in our assumptions about the magnitude and duration of breast cancer risk reduction due to prophylactic oophorectomy.

Conclusions: Life expectancy gains depend on the type of *BRCA* mutation and age at interventions. Sensitivity analysis identifies the degree of breast cancer risk reduction due to prophylactic oophorectomy as a key determinant of life expectancy gain.

Impact: Further study of the impact of prophylactic oophorectomy on breast cancer risk in *BRCA1/2* mutation carriers is warranted. *Cancer Epidemiol Biomarkers Prev; 21(7); 1066–77. ©2012 AACR.*

Introduction

Inherited mutations in the *BRCA1* and *BRCA2* (*BRCA1/2*) cancer susceptibility genes convey high lifetime risks of breast and ovarian cancer, in the range of 40% to 66% and 13% to 46%, respectively (1, 2). Because female *BRCA1/2* mutation carriers have 5- to 40-fold higher cancer risks than average-risk women in the United States, a number of intensive risk-reducing strategies are recommended. These interventions include prophylactic mastectomy, prophylactic oophorectomy, breast cancer screening with a combination of mammography and MRI, and chemoprevention with agents such as tamoxifen and raloxifene (3). Because of the relative rarity of *BRCA1/2* mutation carriers (4, 5), as well as the invasive nature of several of these risk-reducing interventions, no randomized controlled trial has yet showed the efficacy of prophylactic surgery, cancer screening, or chemoprevention in this high-risk population. Thus, there remains significant controversy about the overall health benefits of several risk-reducing strategies in *BRCA1/2* mutation carriers.

Screening guidelines for this high-risk population emphasize the initiation of annual mammograms and contrast-enhanced breast MRI at the age of 25 years (6–8). Because of the poor overall sensitivity of screening mammography among *BRCA1/2* mutations, MRI is often recommended in addition to mammography (8, 9) and is regarded as cost-effective, despite being several times more expensive and increasing the rate of false-positive test results (10).

Bilateral prophylactic mastectomy consists of removing both breasts to reduce the risk of developing breast cancer. Studies estimate a 90% to 95% reduction in breast cancer

Authors' Affiliations: Departments of [1]Radiology, [2]Medicine, and [3]Health Research and Policy, Stanford University School of Medicine, Stanford, California

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B.M. Sigal and D.F. Munoz are co-first authors.

Corresponding Author: Sylvia K. Plevritis, Department of Radiology, Stanford University School of Medicine, Stanford, CA 94305. Phone: 650-498-5261; Fax: 650-723-5795; E-mail: sylvia.plevritis@stanford.edu

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incidence for women with *BRCA1/2* mutations who undergo prophylactic mastectomy (11, 12). Despite its benefits, however, the decision to undergo prophylactic mastectomy is complicated, given its potential effects on body image and quality of life.

Prophylactic oophorectomy consists of removing the ovaries and fallopian tubes bilaterally with the primary intent of preventing ovarian and fallopian tube cancers; observational studies in *BRCA1/2* mutation carriers estimate its efficacy at 80% to 90% (13–15). Studies also report reduction in breast cancer risk with premenopausal prophylactic oophorectomy, with hazard ratios (HR) of 0.3 to 0.5 (12, 16, 17). The large, prospective PROSE study of *BRCA1/2* mutation carriers recently reported an overall mortality reduction, with declines in breast and ovarian cancer–related deaths from early prophylactic oophorectomy (11). However, another study questioned whether *BRCA1* versus *BRCA2* mutation carriers receive equivalent benefits from prophylactic oophorectomy (14), and a large cohort study of premenopausal oophorectomy in the general population found increased mortality, with excess risk of dementia and Parkinson disease (18–20). Moreover, premature menopause yields increased risk of osteoporotic hip fracture and possibly cardiovascular disease (21, 22).

Given conflicting reports about its benefit, and the highly personal nature of the decision to undergo prophylactic surgery, a clear understanding of the impact of prophylactic oophorectomy and prophylactic mastectomy on life expectancy, in the presence of screening with mammography and MRI, has great clinical relevance. Previously, we developed a computer simulation model to estimate survival among *BRCA1/2* mutation carriers undergoing different risk-reducing strategies (23) and adapted this model into an online tool to support shared decision making (24). Here, we provide a detailed technical description of the model and present model-based estimates of the impact of risk-reducing strategies on lifetime expectancy among *BRCA1/2* mutations carriers.

Materials and Methods

We previously developed a Monte Carlo model to simulate the natural history of breast cancer in the average-risk U.S. population, incorporating the effect of screening and treatment interventions (25, 26). We then adapted this model to *BRCA1/2* mutation carriers, including the age-specific elevated breast and ovarian cancer risks unique to this population, and used it to estimate the effectiveness and cost-effectiveness of breast screening with MRI (10). Subsequently, this model was modified to incorporate the impact of prophylactic mastectomy and prophylactic oophorectomy on breast and ovarian cancer incidence and survival (23, 24). We reported an evaluation of this model's estimated survival probabilities for *BRCA1/2* mutation carriers undergoing various risk reduction strategies (23, 24). We now report on the methodology developed for the model's implementation, with emphasis on the effect of prophylactic surgery on life expectancy in *BRCA1/2* mutation carriers. In particular, we present life expectancy estimates for *BRCA1/2* mutation carriers undergoing risk reduction strategies at different ages, with sensitivity analysis focused on specific areas of uncertainty, including cancer incidence in women older than 70 years, and the impact of prophylactic oophorectomy on cancer-specific incidence and mortality.

Impact of prophylactic surgery on breast and ovarian cancer incidence in absence of screening

Impact of prophylactic mastectomy on breast cancer incidence. On the basis of published literature, we assumed a 90% reduction in breast cancer risk after prophylactic mastectomy (12). Because of limitations of our natural history model of breast cancer (described below), we assumed that an asymptomatic patient is detected with a malignant breast tumor at time of prophylactic mastectomy if the tumor diameter is greater than 2 mm; however, if the tumor diameter is less than 2 mm, we assume the patient has a 95% probability of being cured, with only a 5% probability of disease progression after prophylactic mastectomy. Furthermore, first and second primary breast cancers are eradicated by prophylactic mastectomy independently of each other and tumors not eradicated by prophylactic mastectomy are detected at the same age, size, and stage they would have been in the absence of prophylactic mastectomy.

Impact of prophylactic oophorectomy on breast cancer incidence. If a woman's first primary breast cancer would have been symptomatically detected after she undergoes prophylactic oophorectomy, we generate a new age at symptomatic detection by assuming that the annual probability of symptomatic detection of breast cancer after prophylactic oophorectomy at age i ($p_{i,\ \mathrm{PO}}$) is $p_{i,\mathrm{PO}} = p_{i,\mathrm{NoPO}}^{\alpha}$, where i is greater or equal to the age at prophylactic oophorectomy and α is the risk reduction expressed as a hazard ratio. Simulation is conducted to ensure that woman's age at first cancer diagnosis, under the prophylactic oophorectomy scenario, is greater than or equal to her age at first cancer diagnosis in the absence of prophylactic oophorectomy. On the basis of published reports in women with *BRCA1/2* mutations (16), we assumed the HR (α) of 0.5 for women who undergo prophylactic oophorectomy at or after the age of 40 and 0.36 for women who undergo prophylactic oophorectomy before the age of 40. Moreover, prophylactic oophorectomy is assumed to have no effect on breast cancer incidence if the procedure is conducted at age $\geq$50.

In modeling the effect of prophylactic oophorectomy on the second primary breast cancer, we used a similar approach. The time to a second breast cancer after prophylactic oophorectomy was computed from the time of the first breast cancer's diagnosis in the presence of prophylactic oophorectomy, so that the chronologic order of tumors remained unchanged compared with the no prophylactic oophorectomy scenario. We also ensured that the time interval to a second breast tumor in the presence

of prophylactic oophorectomy was no shorter than the same interval under the no prophylactic oophorectomy scenario.

Impact of prophylactic oophorectomy on ovarian cancer incidence. On the basis of published literature (13), we assumed 80% reduction in ovarian cancer risk after prophylactic oophorectomy. Furthermore, as prophylactic oophorectomy removes tissue at risk of developing ovarian cancer, this reduction is treated as a probability of ovarian cancer eradication. If the cancer is not eradicated by prophylactic oophorectomy, we assumed that the age at symptomatic detection is unchanged compared with the scenario of no prophylactic oophorectomy.

Incidence of primary breast and ovarian cancer in absence of risk-reducing interventions

We define the "first primary breast cancer" as the breast cancer that would have been diagnosed first chronologically, due to symptoms, in the absence of any intervention. To model incidence of a first primary breast cancer for *BRCA1/2* mutation carriers, we leveraged a large population-based meta-analysis which estimated the age-specific incidence of breast and ovarian cancer in this population (1). Because age-specific breast and ovarian cancer incidence for women who choose not to undergo prophylactic oophorectomy is a key input to our model and this meta-analysis did not include information on prophylactic oophorectomy use (1), we derived this key model input by assuming that the meta-analysis constituted a mixture of women who chose premenopausal prophylactic oophorectomy and women who did not. In Supplementary Appendix SI, we present the algorithm that we developed to estimate age-specific breast cancer incidence in the absence of risk-reducing interventions.

Incidence of second primary breast cancer in absence of prophylactic mastectomy, prophylactic oophorectomy, and screening

BRCA1/2 mutation carriers have high risks of a second primary breast cancer, once they have been diagnosed with a first breast cancer. On the basis of a prospective cohort study for the subpopulation of *BRCA1* mutation carriers who did not undergo premenopausal oophorectomy or take tamoxifen (11), the 5-year risk of a contralateral second primary breast cancer is 27.1% and the corresponding 10-year risk is 43.4%. For a similar subpopulation of *BRCA2* mutation carriers, the corresponding 5- and 10-year risks are 23.5% and 34.6%, respectively. To model the time to a second primary breast cancer as a continuous variable, we assumed a 2-parameter Weibull distribution and estimated parameters by fitting to 5- and 10-year risks separately for *BRCA1* and *BRCA2* mutation carriers.

Impact of screening on breast cancer incidence and staging

To predict the impact of screening on breast cancer incidence and staging, we model the natural history of the disease and the ability of the screening test to detect the disease before symptoms arise, as in our prior work (10, 26).

Natural history model of breast cancer. The assumptions underlying our natural history model of BRCA1/2-associated breast cancers are similar to those we previously used for the average-risk female U.S. population (26, 27) but incorporate modifications to reflect the histopathologic characteristics of the breast cancers in *BRCA1/2* mutation carriers. We previously reported a detailed description of our assumptions related to tumor growth, tumor volume doubling time (TVDT), and hazard functions characterizing the transition times from local to regional and distant stages and the time of symptomatic detection (26, 27). We also provide an overview of these assumptions and a description of the model's parameters in the Supplementary Appendix SII.

For the average-risk population, we obtained maximum likelihood estimates of our natural history model parameters using data on tumor size and stage at diagnosis obtained from the Surveillance Epidemiology and End Results (SEER) registry in the era before mammographic screening (26). However, clinical studies have found that histopathologic characteristics of BRCA1/2-associated breast cancers, such as hormone receptor status and grade, differ from those of women with sporadic breast cancers. In particular, *BRCA1* mutation carriers are significantly more likely to be diagnosed with grade III, hormone receptor–negative breast cancers than other women (28). Because higher tumor grade is associated with more aggressive clinical behavior, we modeled them as faster growing. In particular, we stratified our natural history model by breast tumor grade: low (grade I–II) versus high (grade III). Model parameter estimation by grade was based on SEER data for women diagnosed at ages 40 to 65 years between 1975 and 1981, using only the records with tumor grade available. The complete set of estimated natural history model parameters for both low- and high-grade tumors may be found in Supplementary Table A.1 of Supplementary Appendix SII.

For parameter identifiability, two constraints were imposed. First, we assumed that for a given TVDT, the distribution of tumor size at symptomatic detection is the same for low- and high-grade tumors. Second, we fixed the mean TVDT for low-grade tumors, which allowed us to compute ratio of the mean TVDT for high-grade to the mean TVDT of low-grade tumors as 0.54.

We derived the absolute values of the mean TVDT for low- and high-grade breast tumors by calibrating to a 1-year sensitivity of breast MRI for a cancer detection of 85% for *BRCA1/2* mutation carriers (29–31). We obtained an overall mean TVDT for *BRCA1* and *BRCA2* mutation carriers by using reported proportions of low- versus high-grade tumors in each population (17, 28, 32).

Because of the absence of empiric data, we assumed that estrogen receptor (ER) status was determined by grade (17, 32). For low-grade tumors, the proportion of ER-positive breast cancers was 91% for *BRCA1* and 94%

for *BRCA2* mutation carriers. On the other hand, for high-grade tumors, the proportion of ER-positive breast cancers was 18% for *BRCA1* and 61% for *BRCA2* mutation carriers. We did not model borderline cases of ER status.

Survival outcomes

Breast cancer survival. From the time of symptomatic diagnosis, we applied breast cancer survival curves for the general U.S. population, using SEER data for ages 40 to 65 in the prescreening era (1975–1981). We stratified these survival curves according to tumor size (<2, 2–5, and ≥5 cm), SEER historic stage (local, regional, distant), and tumor grade (I + II vs. III). We used the same survival curves for first and second primary breast cancer. We took the same approach as described in our prior work to model survival after breast cancer is detected by screening or at the time of prophylactic mastectomy (26).

Ovarian cancer survival. Following ovarian cancer diagnosis, we applied survival curves on the basis of ovarian cancer cases diagnosed during 1975 to 2001, as recorded in the SEER 9 registries. We stratified these curves by 5-year age groups. On the basis of prior publications which have reported on histologic subtypes of ovarian cancers associated with *BRCA1/2* mutations (33–35), we used only the following ICD-O-3 histologic codes: 8000-8001, 8005, 8010, 8020, 8050, 8140, 8230, 8260, 8310, 8380, 8440-8441, 8450, 8460-8461, 8470-8471, and 8480-8481.

Other-cause mortality. We derived mortality from causes other than breast and ovarian cancer from the Berkeley Mortality Tables (36), according to birth cohort and age at death. We modified these tables by subtracting deaths due to breast and ovarian cancer, using 2004 cross-sectional death rates from the Centers for Disease Control (CDC; ref. 37). We translated CDC death rates, which were reported in 5-year age intervals, into single-year rates by linear interpolation under the assumption that reported rates correspond to the middle of the age interval (i.e., ages 22, 27, 32, 37. . .92) and that rates for ages <20 years are equal to 0. Death rates for ages 92+ were held constant. We converted annual probabilities of death (q_i) during age intervals (i, $i + 1$), as reported in the Berkeley Mortality Tables, to death rates (r_i) by assuming exponential distribution: $r_i = -\ln(q_i)$. Then, the annual probability of death from causes other than breast and ovarian cancer was computed as $q_i^{-(\mathrm{BC+OC})} = \exp(-(r_i - r_i^{\mathrm{BC}} - r_i^{\mathrm{OC}}))$.

We modeled an increase in deaths from cardiovascular disease, hip fracture, and dementia after premenopausal prophylactic oophorectomy according to previous reports (18, 20, 21). We used death rates as reported by the CDC (37) in 2004 for the general U.S. population, from cardiovascular disease (r_i^{CV}; ICD-10: I20-I25) and dementia (r_i^{Dem}; ICD-10: F01, F03, G20-G21, G30). We used estimates for death rates because of hip fractures r_i^{Hip} after prophylactic oophorectomy based on a previously published analysis of oophorectomy outcomes (38). For ages greater than or equal to a woman's age at prophylactic oophorectomy, we computed annual other-cause mortality probabilities as:

$$q_{i,PO}^{-(\mathrm{BC+OC})} = \exp\Big(-\big[r_i - r_i^{\mathrm{BC}} - r_i^{\mathrm{OC}} - \big(1-\mathrm{HR}^{\mathrm{CV}}\big)r_i^{\mathrm{CV}} - \big(1-\mathrm{HR}^{\mathrm{Dem}}\big)r_i^{\mathrm{Dem}} - \big(1-\mathrm{HR}^{\mathrm{Hip}}\big)r_i^{\mathrm{Hip}}\big]\Big),$$

where $\mathrm{HR}^{\mathrm{CV}}$, $\mathrm{HR}^{\mathrm{Dem}}$, $\mathrm{HR}^{\mathrm{Hip}}$ are hazard ratios associated with cardiovascular disease (21), dementia (18, 20, 22), and hip fracture (22), respectively.

Sensitivity analysis

In prior work (10, 23, 24), we found that overall survival gain under the various interventions is

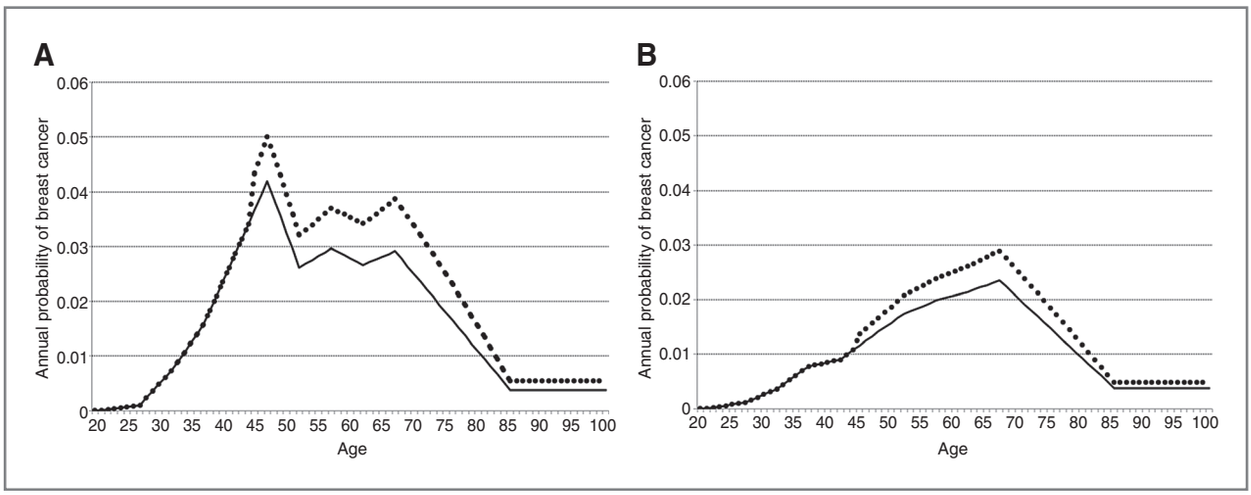

Figure 1. Annual probabilities of first primary breast cancer in the work of Antoniou and colleagues (ref. 1; straight curve) and in the absence of prophylactic oophorectomy (dotted curve) for (A) *BRCA1* mutation carriers and (B) *BRCA2* mutation carriers. Probabilities are kept constant after the age of 85.

Table 1. Gains in life expectancy for *BRCA1/2* mutation carriers after undergoing several risk reduction strategies

	Life expectancy,[a] y					
	***BRCA1* mutation carrier Age at carrier status determination, y**			***BRCA2* mutation carrier Age at carrier status determination, y**		
Strategy	**30**	**40**	**50**	**30**	**40**	**50**
No S and no PM and no PO	41.5	32.7	26.1	48.6	39.4	30.7
Gain in life expectancy, y						
S[b]	2.6	2.2	1.4	1.6	1.4	1.0
PM	5.2	4.3	2.8	3.1	2.7	2.0
PO	7.4	6.1	3.3	3.0	2.4	1.3
PM and PO	10.3	9.1	6.8	4.4	3.9	3.4
S and PO	8.8	7.6	5.1	3.7	3.1	2.4
Gain in life expectancy when prophylactic surgery is delayed by 5 y						
Delayed PM	4.6	3.0	1.7	2.9	2.3	1.3
Delayed PO	7.0	5.0	2.7	2.9	2.2	0.9
Delayed PM and PO	9.6	7.0	4.8	4.1	3.4	2.3
S and delayed PM	4.9	3.7	2.4	3.0	2.5	1.7
S and delayed PO	8.6	6.7	4.4	3.6	3.0	2.0
S and delayed (PM and PO)	9.9	7.8	5.5	4.2	3.6	2.7
Gain in life expectancy when prophylactic surgery is delayed by 10 y						
Delayed PM	3.7	1.8	1.0	2.5	1.7	0.8
Delayed PO	5.5	2.8	2.1	2.3	1.2	0.5
Delayed PM and PO	8.2	5.0	3.2	3.7	3.0	1.4
S and delayed PM	4.4	3.2	2.0	2.8	2.2	1.5
S and delayed PO	7.6	5.3	3.7	3.3	2.7	1.6
S and delayed PM and PO	9.0	6.5	4.4	4.0	3.6	2.0

NOTE: All gains are reported additively to the base life expectancy (first row of table), in which no intervention is conducted.
Abbreviations: PM, prophylactic mastectomy; PO, prophylactic oophorectomy; S, screening.
[a]All results are for a 1980 birth cohort.
[b]Screening (mammography + MRI) starts at the age of BRCA carrier status determination and ends by the age of 70. Annual mammography screening starts at the age of BRCA status determination or age 40, whichever comes first.

sensitive to variations in assumptions about cancer risks, MRI sensitivity for breast cancer diagnosis, and the HR for breast cancer incidence after premenopausal prophylactic oophorectomy. Here we conducted sensitivity analysis on 3 different sets of parameters, namely, those used to calculate: (i) breast cancer incidence estimates obtained by removing the effect of prophylactic oophorectomy from the work of Antoniou and colleagues (1), (ii) cancer incidence after the age of 69, and (iii) the duration of the protective effect of prophylactic oophorectomy on breast cancer risk after surgery. To date, there is no evidence indicating that the protective effect of prophylactic oophorectomy on breast cancer lasts more than 15 years after surgery (16) and little is reported on the breast cancer incidence of *BRCA1/2* mutation carriers at older ages.

The sensitivity analysis conducted on our breast cancer incidence estimates from removing the effect of prophylactic oophorectomy compare the cumulative incidence of breast cancer by the age of 70 when varying assumptions related to the efficacy of the protective effect of prophylactic oophorectomy over breast cancer (α), the age and percentage of women undergoing prophylactic oophorectomy.

The sensitivity analyses regarding cancer incidence after the age of 69 considered 2 scenarios. In scenario A, we assumed that cancer risk beyond this age is similar to that of the general population, based on the SEER registry. In scenario B, we assumed that the risk for this population is still higher than that of the general population; hence, cancer incidence was kept constant for years following the last period (age, 67–69 years) in which *BRCA1/2* mutation–associated incidence was estimated from the work of Antoniou and colleagues (1).

Regarding the duration of the protective effect of prophylactic oophorectomy on risk of breast cancer, our sensitivity analysis varied this parameter from 10 to 15 years after undergoing the procedure. This particular

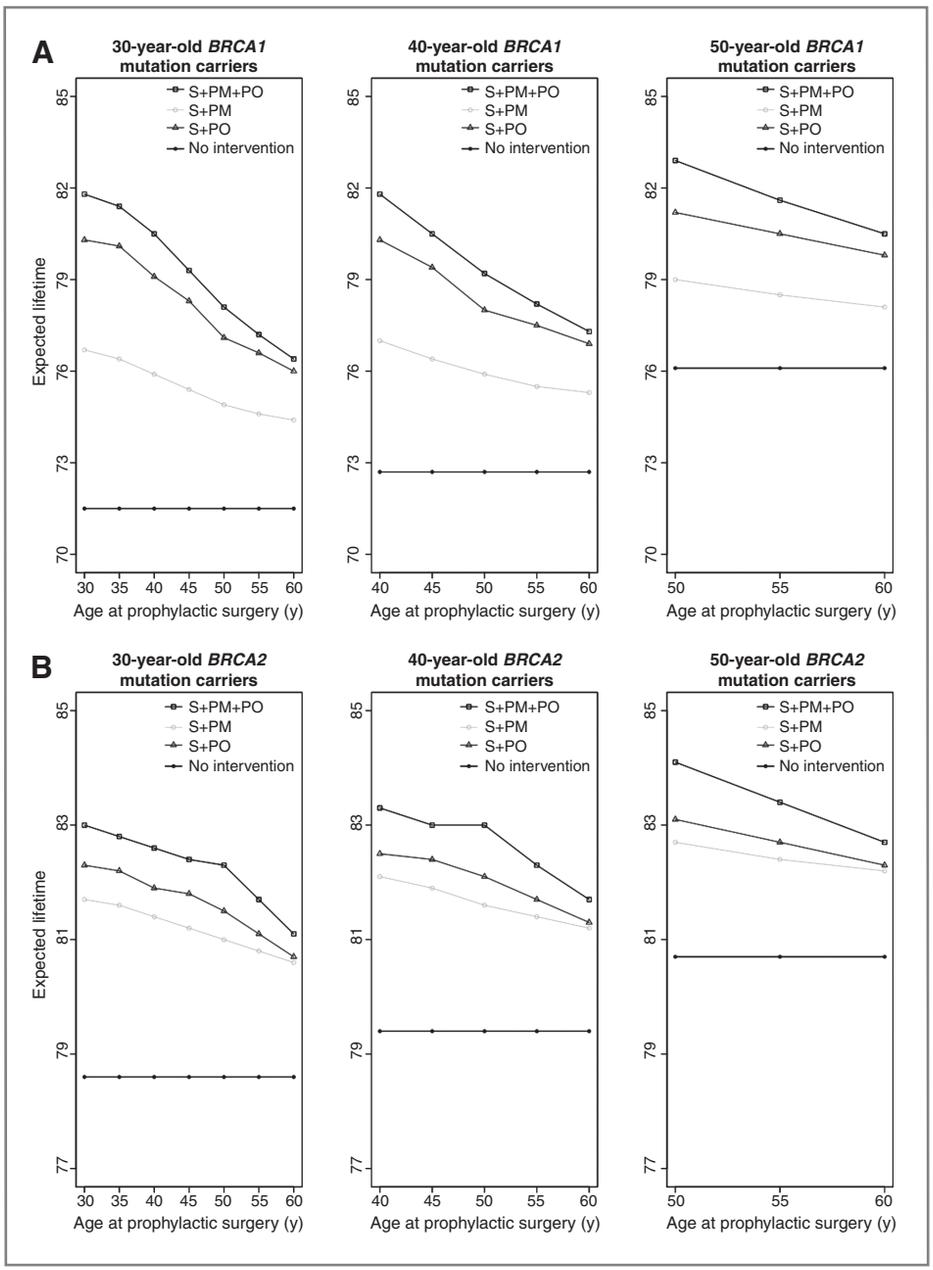

Figure 2. Life expectancy of 30-, 40-, and 50-year-old *BRCA1* (A) and *BRCA2* (B) mutation carriers under different strategies, including prophylactic mastectomy (PM), prophylactic oophorectomy (PO), and screening with mammography and MRI (S). All scenarios include screening starting at the age of BRCA carrier status determination and ending at age of PM or age 70, whichever comes first. For all ages, the "No intervention" scenario (black line with solid dots) shows the baseline life expectancy if no intervention is pursued.

sensitivity analysis required use of the algorithm reported in the Methods section to remove the effect of prophylactic oophorectomy and compute annual age-specific breast cancer incidences for each case.

Results

Annual probabilities of a first primary breast cancer in absence of risk-reducing interventions

Figure 1A and B shows the estimated annual probabilities of a first primary breast cancer in the absence of risk-reducing interventions for *BRCA1* and *BRCA2* mutation carriers, respectively. Compared with the breast cancer risk in the work of Antoniou and colleagues, we report a greater cumulative risk of breast cancer by the age of 70 (0.65 vs. 0.71 for *BRCA1* and 0.45 vs. 0.50 for *BRCA2* mutation carriers) because we removed the protective effect of premenopausal prophylactic oophorectomy on subsequent breast cancer risk.

Impact of prophylactic surgery and screening on life expectancy

Table 1 shows the gains in life expectancy resulting from prophylactic intervention and screening, for *BRCA1* and *BRCA2* mutation carriers, when simulating one

Table 2. Sensitivity analysis on the cumulative probability of breast cancer by the age of 70 for *BRCA1* and *BRCA2* mutation carriers in the absence of risk-reducing interventions

	Cumulative probability of breast cancer by the age of 70 in absence of risk reduction interventions (%),[a]					
	BRCA1 mutation carrier PO hazard ratio risk reduction on breast cancer incidence (α),[a]			*BRCA2* mutation carrier PO hazard ratio risk reduction on breast cancer incidence (α),[a]		
Age at PO	**0.2**	**0.5**	**0.8**	**0.2**	**0.5**	**0.8**
0% of women had undergone PO in study of Antoniou and colleagues (1)						
	66			**46**		
30% of women had undergone PO in study of Antoniou and colleagues (1)						
Age at PO: 40	68	73	82	48	52	57
Age at PO: 45	68	72[b]	79	47	51[b]	56
Age at PO: 50	67	71	76	47	50	55
70% of women had undergone PO in study of Antoniou and colleagues (1)						
Age at PO: 40	71	81	97	50	61	80
Age at PO: 45	70	80	95	50	60	78
Age at PO: 50	69	77	91	49	58	76
100% of women had undergone PO in study of Antoniou and colleagues (1)						
Age at PO: 40	73	87	99	53	68	94
Age at PO: 45	71	84	98	52	67	93
Age at PO: 50	70	81	97	51	65	90

NOTE: Sensitivity analysis when using the algorithm presented in Supplementary Appendix SI and varying prophylactic oophorectomy risk reduction (α) and the age and percentage of women who had undergone prophylactic oophorectomy in the study of Antoniou and colleagues (1).

Abbreviations: PM, prophylactic mastectomy; PO, prophylactic oophorectomy.

[a]See Supplementary Appendix SI.

[b]Base case scenario (See Supplementary Appendix SI).

million women for each model run. Because of differences in the annual incidence of breast and ovarian cancer, gains in life expectancy from prophylactic mastectomy and prophylactic oophorectomy are highly dependent on the mutated gene (*BRCA1* vs. *BRCA2*) and age at the time of the intervention. With no intervention, the remaining life expectancy of a 30-, 40-, and 50-year-old *BRCA1* mutation carrier who has never had cancer is 41.5, 32.7, and 26.1 years, respectively; the remaining life expectancies of *BRCA2* mutation carriers of the same ages are 48.6, 39.4, and 30.7 years. We present the effect of a single risk-reducing strategy as well as the effect of combining different strategies. For example, the life expectancy gain for 30-year-old *BRCA1* mutation carriers is 5.2, 7.4, or 10.3 years, if she chooses prophylactic mastectomy alone, prophylactic oophorectomy alone, or both, respectively.

Given that many women may delay prophylactic mastectomy and prophylactic oophorectomy due to reproductive or personal preferences, we present the gains in life expectancy when the prophylactic procedures are delayed 5 or 10 years after carrier status determination. Figure 2A and B compares the life expectancies of 30-, 40-, and 50-year-old *BRCA1* and *BRCA2* mutation carriers, respectively, under different strategies, when screening is initiated from the time of BRCA status determination (mammography at age 40 if age at status determination is >40) until the age of 70 and prophylactic surgery is conducted at various ages up to the age of 60.

Delaying prophylactic surgery from age 30 to 40, a comparatively low-risk decade for *BRCA1/2* mutation carriers, does not affect life expectancy as much as would a longer delay. For example, if a *BRCA1* mutation carrier of age 30 delays prophylactic oophorectomy for 10 years, she forfeits an expected gain of 1.9 years (7.4 vs. 5.5 years); in comparison, for a 40-year-old, a 10-year delay costs 3.3 years of life expectancy (6.1 vs. 2.8 years).

Sensitivity analysis

Table 2 shows the sensitivity analysis conducted by varying the parameters used to calculate breast cancer incidence in the absence of risk-reducing interventions. We varied presumed percentage of prophylactic oophorectomy and age at prophylactic oophorectomy in the meta-analysis cohort of Antoniou and colleagues (1) and reported the cumulative probability of breast cancer by the age of 70. For example, we obtain a 76% probability of developing breast cancer for *BRCA1* mutation carriers when 30% of women at age 50 years underwent

Table 3. Sensitivity analysis on gains in life expectancy for *BRCA1* and *BRCA2* mutation carriers when varying assumption related to breast cancer incidence after the age of 69

	Life expectancy y[a]					
	***BRCA1* mutation carrier Age at carrier status determination and incidence scenario**			***BRCA2* mutation carrier Age at carrier status determination and incidence scenario**		
Strategy	**30 base case[b]**	**30 scenario A,[c]**	**30 scenario B,[d]**	**30 base case[b]**	**30 scenario A,[c]**	**30 scenario B,[d]**
No S and no PM and no PO	41.5	41.7	41.4	48.6	48.8	48.5
Gain in life expectancy, y						
S[a]	2.6	2.6	2.6	1.6	1.6	1.6
PM	5.2	5.1	5.3	3.1	3.0	3.3
PO	7.4	7.4	7.4	3.0	3.0	3.1
PM and PO	10.3	10.2	10.4	4.4	4.2	4.5
S and PO	8.8	8.8	8.8	3.7	3.6	3.8
Gain in life expectancy when prophylactic surgery is delayed by 5 y						
Delayed PM	4.6	4.5	4.7	2.9	2.7	3.0
Delayed PO	7.0	7.0	7.0	2.9	2.8	3.0
Delayed PM and PO	9.6	9.4	9.7	4.1	3.9	4.3
S and delayed PM	4.9	4.7	5.0	3.0	2.8	3.1
S and delayed PO	8.6	8.5	8.6	3.6	3.5	3.7
S and delayed PM and PO	9.9	9.7	10.0	4.2	4.1	4.4
Gain in life expectancy when prophylactic surgery is delayed by 10 y						
Delayed PM	3.7	3.6	3.8	2.5	2.3	2.7
Delayed PO	5.5	5.6	5.5	2.3	2.2	2.3
Delayed PM and PO	8.2	8.1	8.3	3.7	3.5	3.8
S and delayed PM	4.4	4.3	4.5	2.8	2.6	2.9
S and delayed PO	7.6	7.6	7.6	3.3	3.2	3.3
S and delayed PM and PO	9.0	8.9	9.1	4.0	3.8	4.3

NOTE: All gains are reported in addition to the base life expectancy (first row of table), in which no intervention is conducted. Assumptions underlying results are: age at genetic testing for *BRCA1/2* mutations is at age 30. and the cancer incidence rates beyond age 69 years are: base case, scenario A, and scenario B.

Abbreviations: PM, prophylactic mastectomy; PO, prophylactic oophorectomy; S, screening.

[a]All results are for a 1980 birth cohort. [b]: Base case: cancer risk beyond the age of 69 is interpolated between ages 69 and 85 to match the general population risk at age 85, and kept constant after age 85 (See Supplementary Appendix SI).

[c]Scenario A: cancer risk beyond the age of 69 is similar to that of the general population, based on the SEER registry.

[d]Scenario B: cancer risk beyond the age of 69 is assumed constant for the last year in which *BRCA1/2* mutation–associated incidence is estimated.

prophylactic oophorectomy and its protective effect had a hazard reduction of 0.8. We find that the cumulative breast cancer incidence by the age of 70 is highly sensitive to variations in the protective effect of prophylactic oophorectomy on breast cancer incidence and the percentage of women with *BRCA1/2* mutations who underwent prophylactic oophorectomy. The estimates for breast cancer incidence by the age of 70 are less sensitive to the age at which prophylactic oophorectomy is conducted, in part, because the tested age range is quite narrow. We chose to vary this parameter only between ages 40 and 50 because prophylactic oophorectomy is not likely to be conducted before the age of 40 and has been reported to have a small effect on breast cancer incidence for postmenopausal women, typically older than 50 (16).

Results presented in Table 3 show sensitivity of the different risk-reducing procedures to the variation in the breast cancer incidence among the older women. It is assumed that age of *BRCA1/2* mutation status determination is fixed at 30 years. The effect on life expectancy of the different assumptions on the breast cancer incidence in older women (age > 69 years) does not exceed 0.2 years as compared with the base case (0.3 years for *BRCA2* screening and 10 years delayed prophylactic mastectomy and prophylactic oophorectomy). As is expected for scenario A, where incidence for older women is similar to that of average risk population, the effect of prophylactic procedures is smaller than that for the base case. In Table 4, we present sensitivity of the effectiveness of different risk-reducing strategies to varying assumptions on the

Table 4. Sensitivity analysis on gains in life expectancy for *BRCA1* and *BRCA2* mutation carriers as duration of protective effect from prophylactic oophorectomy is varied

	Life expectancy, y					
	Age at BRCA carrier status determination and number of years of post-oophorectomy protective effect					
Strategy	**30, Lifetime PO protective effect**	**30, 10 year PO protective effect**	**30, 15 year PO protective effect**	**40, Lifetime PO protective effect**	**40, 10 year PO protective effect**	**40, 15 year PO protective effect**
***BRCA1* mutation carrier**						
No S and no PM and no PO	41.5	41.6	41.5	32.7	32.9	32.9
Gain in life expectancy, y						
PO	7.4	4.4	4.9	6.1	4.8	5.2
PM and PO	10.3	10.0	10.1	9.1	8.9	8.9
S and PO	8.8	7.2	7.5	7.6	6.8	7.0
Gain in life expectancy when prophylactic surgery is delayed by 5 y						
Delayed PO	7.0	4.6	5.3	5.0	4.2	4.5
Delayed PM and PO	9.6	9.3	9.4	7.0	6.8	6.9
S and delayed PO	8.6	7.2	7.6	6.7	6.2	6.4
S and delayed PM and PO	9.9	9.6	9.7	7.8	7.6	7.7
Gain in life Expectancy when prophylactic surgery is delayed by 10 y						
Delayed PO	5.5	4.5	4.8	2.8	2.8	2.8
Delayed PM and PO	8.2	8.0	8.1	5.0	4.8	4.9
S and delayed PO	7.6	7.0	7.2	5.3	5.3	5.3
S and delayed PM and PO	9.0	8.8	8.9	6.5	6.3	6.4
	Life expectancy, y					
	Age at BRCA carrier status determination and number of years of post-oophorectomy protective effect					
Strategy	**30, Lifetime PO protective effect**	**30, 10-year PO protective effect**	**30, 15-year PO protective effect**	**40, Lifetime PO protective effect**	**40, 10-year PO protective effect**	**40, 15-year PO protective effect**
***BRCA2* mutation carrier**						
No S and no PM and no PO	48.6	48.8	48.8	39.4	39.6	39.5
Gain in life expectancy, y						
PO	3.0	1.3	1.5	2.4	1.4	1.6
PM and PO	4.4	4.1	4.2	3.9	3.7	3.7
S and PO	3.7	2.7	2.8	3.1	2.5	2.7
Gain in life expectancy when prophylactic surgery is delayed by 5 y						
Delayed PO	2.9	1.4	1.6	2.2	1.5	1.7
Delayed PM and PO	4.1	3.8	3.9	3.4	3.2	3.3
S and delayed PO	3.6	2.7	2.9	3.0	2.5	2.7
S and delayed PM & PO	4.2	4.0	4.0	3.6	3.4	3.5
Gain in life expectancy when prophylactic surgery is delayed by 10 y						
Delayed PO	2.3	1.3	1.6	1.2	1.2	1.2
Delayed PM and PO	3.7	3.5	3.5	3.0	2.8	2.9
S and delayed PO	3.3	2.7	2.9	2.7	2.6	2.6
S and delayed PM and PO	4.0	3.8	3.9	3.6	3.4	3.4

NOTE: All gains are reported in addition to the base life expectancy, in which no intervention is conducted. Assumptions underlying results are ages at genetic testing for *BRCA1/2* mutations are 30 and 40 years; the duration of PO's impact on breast cancer risk reduction is: lifetime, 10 years and 15 years, respectively.

Abbreviations: PM, prophylactic mastectomy; PO, prophylactic oophorectomy; S, screening.

duration of the prophylactic oophorectomy protective effect on the breast cancer incidence. This sensitivity analysis was conducted under the assumption that age of *BRCA1/2* mutation status determination is 30 and 40. Assuming a 10-year window of breast cancer risk reduction from prophylactic oophorectomy, a 30-year-old *BRCA1* mutation carrier gains 4.4 years from immediate prophylactic oophorectomy, whereas 5- and 10-year delays offer slight gains of 4.6 and 4.5 years, respectively.

Discussion

We report on the gains in life expectancy from conducting prophylactic surgery and screening among women with *BRCA1/2* mutations, at different ages of genetic testing and risk-reducing interventions. In general, the observed gain in life expectancy from premenopausal prophylactic oophorectomy is greater than that provided by prophylactic mastectomy, as prophylactic oophorectomy reduces the risk of both breast and ovarian cancer. However, screening with annual mammography plus breast MRI provides significant gains in life expectancy, although its benefits are less than those of prophylactic mastectomy or prophylactic oophorectomy.

The greatest life expectancy gain is provided by prophylactic mastectomy + prophylactic oophorectomy at the time of genetic testing for *BRCA1/2* mutations. We found that gains in life expectancy are highly dependent on the timing of prophylactic surgery. However, delaying prophylactic surgery can still provide an important gain in life expectancy, especially in tandem with annual breast screening.

In sensitivity analysis, assuming a limited duration for prophylactic oophorectomy's reduction in breast cancer risk renders timing even more critical: prophylactic oophorectomy can provide an equivalent or greater life expectancy increase when timed to affect the years of high risk. The impact of prophylactic oophorectomy on breast cancer risk reduction was the most influential variable in our sensitivity analysis.

Several prior studies have investigated the impact of prophylactic mastectomy and prophylactic oophorectomy on survival of *BRCA1/2* mutation carriers (39–43). Most used a Markov model for decision analysis, which is conceptually different from the approach of explicitly modeling cancer growth and progression that was adopted here. Our modeling approach is closest to that of Schrag and colleagues (43) who reported a comparable life expectancy gain from prophylactic mastectomy at 2.9 to 5.3 years for 30-year-old women but a lower gain from prophylactic oophorectomy (0.3–1.7 years), likely due to their assumption that prophylactic oophorectomy reduces ovarian, but not breast cancer risk; other early articles showed similar results (40, 43). More recent studies suggest that *BRCA1* mutation carriers benefit more from prophylactic oophorectomy than prophylactic mastectomy, with the reverse finding for *BRCA2* mutation carriers (39, 41); our results agree with the exception that we report a larger life expectancy gain from prophylactic oophorectomy. Consistent with other studies, we find a greater life expectancy from prophylactic mastectomy or prophylactic oophorectomy than from breast screening alone (41), although the life expectancy afforded by annual screening mammography plus breast MRI is significant, particularly in combination with prophylactic oophorectomy. The recent simulation model–based study (42) investigated effect of different screening modalities and strategies alone, including MRI, film and digital mammography on the life expectancy of the *BRCA1/2* mutation carriers. In that study, the maximum gain of 1.86 years for *BRCA1* (range, 1.3–1.86) and 1.76 years (range, 1.46–1.76) for *BRCA2* mutation carriers was attained for alternating digital mammography with MRI at 6 months intervals starting at the age of 25. Results are comparable with our results for *BRCA2* and somewhat lower for *BRCA1* mutation carriers.

We used simulation modeling to estimate the life expectancy of women with *BRCA1/2* mutations who chose to undergo prophylactic surgery for cancer risk reduction at various ages. To address limitations of our model-based approach, we conducted sensitivity analysis on deep model parameters. In prior work, we identified limitations in clinical assumptions of our model (10, 23, 24). Of note, chemoprevention is not included in our current analysis as an alternative to prophylactic surgery because its efficacy is still being evaluated among mutation carriers. Despite limitations of simulation modeling, it may offer the most practical approach to urgent questions for patient care when randomization is infeasible. Our model integrates existing data to quantify the overall effect of cancer risk-reducing strategies, readily incorporates emerging data, and enables a risk–benefit calculation customized for an individual woman's age and *BRCA1/2* mutation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: B.M. Sigal, A.W. Kurian, S.K. Plevritis
Development of methodology: B.M. Sigal, D.F. Munoz, S.K. Plevritis
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D.F. Munoz, S.K. Plevritis
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): B.M. Sigal, D.F. Munoz, S.K. Plevritis
Writing, review, and/or revision of the manuscript: B.M. Sigal, D.F. Munoz, A.W. Kurian, S.K. Plevritis
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D.F. Munoz, S.K. Plevritis
Study supervision: S.K. Plevritis

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References

1. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117–30.
2. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25:1329–33.
3. National Comprehensive Cancer Network. Genetic/familial high-risk assessment: breast and ovarian. V. 1.2011. Fort Washington, PA: NCCN. [cited 2011 Jul]. Available from: http://www.nccn.org.
4. John EM, Miron A, Gong G, Phipps AI, Felberg A, Li FP, et al. Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA 2007;298:2869–76.
5. Tengs TO, Winer EP, Paddock S, Aguilar-Chavez O, Berry DA. Testing for the BRCA1 and BRCA2 breast-ovarian cancer susceptibility genes: a decision analysis. Med Decis Making 1998;18:365–75.
6. National Comprehensive Cancer Network Guidelines for genetic/familial high-risk assessment: breast and ovarian. Fort Washington, PA: NCCN. [cited 2011 Jul]. Available from: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf.
7. Kuhl CK, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 2005;23:8469–76.
8. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75–89.
9. National Comprehensive Cancer Network. Breast cancer screening and diagnosis V.1.20011. Fort Washington, PA: NCCN. [cited 2011 Jul]. Available from: http://www.nccn.org.
10. Plevritis SK, Kurian AW, Sigal BM, Daniel BL, Ikeda DM, Stockdale FE, et al. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. JAMA 2006;295:2374–84.
11. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328–35.
12. Rebbeck TR, Friebel T, Lynch HT, Neuhausen SL, van 't Veer L, Garber JE, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2004;22:1055–62.
13. Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA 2006;296:185–92.
14. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609–15.
15. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346:1616–22.
16. Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol 2005;23:7491–6.
17. Foulkes WD, Metcalfe K, Sun P, Hanna WM, Lynch HT, Ghadirian P, et al. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. Clin Cancer Res 2004;10:2029–34.
18. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 2007;69:1074–83.
19. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology 2008;70:200–9.
20. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ III. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol 2006;7:821–8.
21. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987;316:1105–10.
22. Melton LJ III, Khosla S, Malkasian GD, Achenbach SJ, Oberg AL, Riggs BL. Fracture risk after bilateral oophorectomy in elderly women. J Bone Miner Res 2003;18:900–5.
23. Kurian AW, Sigal BM, Plevritis SK. Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers. J Clin Oncol 2010;28:222–31.
24. Kurian AW, Munoz DF, Rust P, Schackmann EA, Smith M, Clarke L, et al. Online tool to guide decisions for BRCA1/2 mutation carriers. J Clin Oncol 2012;30:497–506.
25. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784–92.
26. Plevritis SK, Sigal BM, Salzman P, Rosenberg J, Glynn P. A stochastic simulation model of U.S. breast cancer mortality trends from 1975 to 2000. J Natl Cancer Inst Monogr 2006;86–95.
27. Plevritis SK, Salzman P, Sigal BM, Glynn PW. A natural history model of stage progression applied to breast cancer. Stat Med 2007;26:581–95.
28. Chappuis PO, Nethercot V, Foulkes WD. Clinico-pathological characteristics of BRCA1- and BRCA2-related breast cancer. Semin Surg Oncol 2000;18:287–95.
29. Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004;351:427–37.
30. Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365:1769–78.
31. Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004;292:1317–25.
32. Tung N, Wang Y, Collins LC, Kaplan J, Li H, Gelman R, et al. Estrogen receptor positive breast cancers in BRCA1 mutation carriers: clinical risk factors and pathologic features. Breast Cancer Res 2010;12:R12.
33. Evans DG, Young K, Bulman M, Shenton A, Wallace A, Lalloo F. Probability of BRCA1/2 mutation varies with ovarian histology: results from screening 442 ovarian cancer families. Clin Genet 2008;73:338–45.
34. Lakhani SR, Manek S, Penault-Llorca F, Flanagan A, Arnout L, Merrett S, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. Clin Cancer Res 2004;10:2473–81.
35. Werness BA, Ramus SJ, DiCioccio RA, Whittemore AS, Garlinghouse-Jones K, Oakley-Girvan I, et al. Histopathology, FIGO stage, and BRCA mutation status of ovarian cancers from the Gilda Radner Familial Ovarian Cancer Registry. Int J Gynecol Pathol 2004;23:29–34.
36. Berkeley Mortality Database. [cited 2008 Aug 4]. Available from: http://www.demog.berkeley.edu/~bmd/States/ssa/life.tables/ufgen.lt.1×1%5D.
37. CDC/NCHS, National Vital Statistics System, Worktable 292R. Death rates for 358 selected causes by 5-year age groups, race, and sex: United States, 1999–2004. [cited 2008 Aug 4]. Available from: http://www.cdc.gov/nchs/data/dvs/mortfinal2004_worktable292r.pdf.
38. Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. Obstet Gynecol 2005;106:219–26.
39. Anderson K, Jacobson JS, Heitjan DF, Zivin JG, Hershman D, Neugut AI, et al. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. Ann Intern Med 2006;144:397–406.
40. Grann VR, Panageas KS, Whang W, Antman KH, Neugut AI. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. J Clin Oncol 1998;16:979–85.

41. Grann VR, Patel PR, Jacobson JS, Warner E, Heitjan DF, Ashby-Thompson M, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. Breast Cancer Res Treat 2011;125:837–47.
42. Lowry KP, Lee JM, Kong CY, McMahon PM, Gilmore ME, Cott Chubiz JE, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. Cancer 2012;118:2021–30.
43. Schrag D, Kuntz KM, Garber JE, Weeks JC. Decision analysis–effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. N Engl J Med 1997;336:1465–71.