VOLUME 30 · NUMBER 5 · FEBRUARY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Online Tool to Guide Decisions for *BRCA1/2* Mutation Carriers

Allison W. Kurian, Diego F. Munoz, Peter Rust, Elizabeth A. Schackmann, Michael Smith, Lauren Clarke, Meredith A. Mills, and Sylvia K. Plevritis

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Allison W. Kurian, Diego F. Munoz, Elizabeth A. Schackmann, Meredith A. Mills, and Sylvia K. Plevritis, Stanford University School of Medicine, Stanford, CA; Peter Rust, Michael Smith, and Lauren Clarke, Cornerstone Systems Northwest, Lynden, WA.

Submitted July 28, 2011; accepted October 20, 2011; published online ahead of print at www.jco.org on January 9, 2012.

Supported by the National Institutes of Health (Grants No. R01 CA829040, U01 CA088248, and R01 CA66785 to S.K.P), the Robert Wood Johnson Foundation (Physician Faculty Scholars Award, Grant No. 64317 to A.W.K.), and a Stanford Cancer Institute Developmental Research Award.

Presented in part at the Robert Wood Johnson Foundation Physician Faculty Scholars Meeting, December 8-10, 2010, Fort Lauderdale, FL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Sylvia K. Plevritis, PhD, Department of Radiology, Stanford University School of Medicine, Lucas MRS Imaging Center, Room P267, Stanford, CA 94305-5488; e-mail: sylvia.plevritis@stanford.edu.

0732-183X/12/3005-497/$20.00

DOI: 10.1200/JCO.2011.38.6060

ABSTRACT

Purpose
Women with *BRCA1* or *BRCA2* (*BRCA1/2*) mutations must choose between prophylactic surgeries and screening to manage their high risks of breast and ovarian cancer, comparing options in terms of cancer incidence, survival, and quality of life. A clinical decision tool could guide these complex choices.

Methods
We built a Monte Carlo model for *BRCA1/2* mutation carriers, simulating breast screening with annual mammography plus magnetic resonance imaging (MRI) from ages 25 to 69 years and prophylactic mastectomy (PM) and/or prophylactic oophorectomy (PO) at various ages. Modeled outcomes were cancer incidence, tumor features that shape treatment recommendations, overall survival, and cause-specific mortality. We adapted the model into an online tool to support shared decision making.

Results
We compared strategies on cancer incidence and survival to age 70 years; for example, PO plus PM at age 25 years optimizes both outcomes (incidence, 4% to 11%; survival, 80% to 83%), whereas PO at age 40 years plus MRI screening offers less effective prevention, yet similar survival (incidence, 36% to 57%; survival, 74% to 80%). To characterize patients' treatment and survivorship experiences, we reported the tumor features and treatments associated with risk-reducing interventions; for example, in most *BRCA2* mutation carriers (81%), MRI screening diagnoses stage I, hormone receptor-positive breast cancers, which may not require chemotherapy.

Conclusion
Cancer risk-reducing options for *BRCA1/2* mutation carriers vary in their impact on cancer incidence, recommended treatments, quality of life, and survival. To guide decisions informed by multiple health outcomes, we provide an online tool for joint use by patients with their physicians (http://brcatool.stanford.edu).

J Clin Oncol 30:497-506. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Women with *BRCA1* and *BRCA2* (*BRCA1/2*) mutations face substantially elevated lifetime risks of developing breast and ovarian cancer.[1,2] The last decade of research with this high-risk population has identified preventive strategies that save lives, notably early bilateral salpingo-oophorectomy,[3-6] and screening regimens incorporating magnetic resonance imaging (MRI) that diagnose most breast cancers early.[7-12] Although randomized trials have not been performed, studies have reported on breast and ovarian cancer incidence, tumor biologic and clinical features, and quality of life with prophylactic and surveillance interventions for *BRCA1/2* mutation carriers.[1,2,13-23]

Despite substantial progress in managing the cancer risks owing to a *BRCA1/2* mutation, patients and their physicians struggle with choices about interventions, such as whether to replace breast screening with bilateral prophylactic mastectomy (PM) and when to pursue PM and/or prophylactic bilateral salpingo-oophorectomy (PO). Evidence-based practice guidelines recommend PO by age 40 years, but advise physicians and patients to discuss the options of PM versus MRI-based breast screening.[24] Guiding decisions about these interventions is difficult, because no trials have compared them directly. We and others have used decision analysis to compare screening and prophylactic surgery in terms of survival and cost-effectiveness.[25-33] However, prior studies have not fully characterized the patient experience with different interventions—for example, the likelihood that a woman who chooses breast

Table 1. Computer Simulation Model Input Parameters on Cancer Incidence, RR, Screening, and Treatment

	BRCA1	*BRCA2*	Range for Sensitivity Analyses	Source
Breast Cancer Incidence and RR				
Cumulative breast cancer incidence by age 70 years*	0.65	0.45	0.47-0.85 (*BRCA1*); 0.4-0.85 (*BRCA2*)	1,2,37-39
10-year incidence of second primary breast tumor	0.43	0.35	Not varied	18
RR for breast cancer with PM†	0.9	0.9	Not varied	19
RR for breast cancer with PO by age at PO, years‡			0, 0.9‡	4,40,41
25	0.36	0.36		
40-50	0.50	0.50		
≥ 50	None	None		
Duration of RR for breast cancer after PM and PO	Lifelong	Lifelong	Not varied	40,41
Ovarian cancer incidence and RR				
Cumulative ovarian cancer incidence by age 70 years	0.39	0.11	0.39-0.46 (*BRCA1*); 0.11-0.27 (*BRCA2*)	1,2,37-39
RR for ovarian cancer from PO	0.8	0.8	Not varied	4,6,42
Breast cancer characteristics at symptomatic detection (no screening)				
Distribution of tumor grade			Not varied	15,23
1-2	0.22	0.53		
3	0.78	0.47		
Distribution of ER positivity, conditional on grade			Not varied	15,23
1-2	0.91	0.94		
3	0.18	0.61		
Distribution of tumor size, cm			Not varied	Estimated§
< 2	0.29	0.33		
2-5	0.55	0.54		
> 5	0.16	0.13		
Distribution of tumor stage			Not varied	Estimated§
Local	0.43	0.47		
Regional	0.49	0.46		
Distant	0.08	0.07		
Mean TVDT,‖ months	5.7	6.8	Not varied	43
Screening test and protocol characteristics				
Screening interval, years	1	1	Not varied	Assumed
Ages of annual mammography screening, years	25-69	25-69	Not varied	Assumed
Ages of annual MRI screening, years	25-69	25-69	Not varied	Assumed
Sensitivity of MRI screening for cancer detection	85%	85%	50%, 90%	9,10,12,44,45
MRI tumor size detection threshold, cm	0.5	0.5	0.3 cm, 1.53 cm	12,31
Mammography median tumor size detection threshold, cm¶	1	1	Not varied	10,31
Proportion of tumors undetectable by mammography, age in years			Not varied	Estimated#
< 50	0.66	0.66		
≥ 50	0.3	0.3		
RR for breast cancer death after adjuvant systemic therapy				
Adjuvant multiagent chemotherapy, by age in years			Not varied	46
< 50	0.47	0.47		
≥ 50	0.31	0.31		
Adjuvant hormonal therapy, for ER-positive breast cancers	0.31	0.31	Not varied	46
Relative risk for other-cause mortality after PO				
Death resulting from cardiovascular disease	2.0	2.0	Not varied	47
Death related to hip fracture	1.5	1.5	Not varied	48
Death related to dementia	1.5	1.5	Not varied	49,50

NOTE. Adapted from Kurian et al.[29]

Abbreviations: ER, estrogen receptor; MRI, magnetic resonance imaging; PM, prophylactic mastectomy; PO, prophylactic oophorectomy; RR, risk reduction; SEER, Surveillance, Epidemiology, and End Results; TVDT, tumor volume doubling time.

*Reported lifetime breast cancer risks were assumed to have incorporated a 30% background rate of PO at the age of 45 years[42]; time to second breast cancer was modeled with a Weibull distribution.

†We assumed that the reduction in the probability of developing breast cancer after PM was 0.95 (a 95% reduction) per tumor; given the high risk of multiple primary tumors in *BRCA1/2* mutation carriers, the overall reduction in probability of developing breast cancer after PM was 0.9 (a 90% reduction).[18]

‡In the base case, we assumed a hazard ratio of 0.5 (a proportional hazard reduction of 50%) for subsequent breast cancer in women undergoing PO between ages 40 and 50 years.[40] In sensitivity analyses, we evaluated the assumptions that PO had no effect on subsequent breast cancer risk (hazard ratio of 1.0 for women of all ages) and that PO conveyed a hazard ratio of 0.1 for all women undergoing the procedure before age 50 years (a proportional hazard reduction of 90%). We assumed no reduction in the hazard ratio of breast cancer for women undergoing PO at or after age 50 years.

§Derived from our breast cancer natural history model using SEER registry data from 1975 to 1981. Tumor stage categories are derived from SEER and defined as follows: local (tumor is confined to breast and does not involve regional lymph nodes), regional (tumor involves breast and regional lymph nodes), distant (tumor has metastasized to distant organs).

‖The mean TVDT was estimated by calibrating to approximately 85% sensitivity of screening breast MRI in the population with *BRCA1* mutations,[9,10,12,44,45] based on the condition that the mean TVDT of grade 3 tumors is approximately 0.54 times the mean TVDT of grade 1 to 2 tumors, which we derived analytically.

¶The median mammography threshold applies only among women whose tumor is detectable by mammography.

#Estimated by calibrating to mammographic screening sensitivity, which was assumed to be 0.25 under age 50 years,[10] and 0.5 at age ≥ 50 years. Tumors ≥ 5 cm were assumed always to be detectable by mammography.

screening will develop a cancer requiring adjuvant chemotherapy—although cancer treatments significantly impact quality of life and survivorship[34-36] and may inform choices between risk-reduction strategies. Moreover, there is no practical way to compare multiple clinically relevant options, such as immediate PM and PO versus screening plus immediate PO and delayed PM, for an individual patient in real time.

We adapted a previously developed Monte Carlo simulation model to compare breast and ovarian cancer incidence, tumor prognostic features, recommended treatments, overall survival, and cause-specific mortality for *BRCA1/2* mutation carriers. We translated this model into an online clinical decision support tool, enabling personalized cancer risk management for women with *BRCA1/2* mutations.

METHODS

We developed a computer simulation model that integrates published data (Table 1) to estimate breast and ovarian cancer incidence and tumor prognostic features, probability of survival to ages 70 and 80 years, and causes of death for women with a *BRCA1* or *BRCA2* mutation, starting from age 25 years.[29] Risk-reducing interventions were modeled alone and in combination, at ages specified by practice guidelines[24,51]: breast screening consisting of mammography plus MRI started at age 25 years and continued annually to age 69 years, and PM and PO were modeled at ages 25, 40, and 50 years.

Monte Carlo Simulation Model

We initially built and validated a Monte Carlo model to analyze the effects of screening and treatment on the outcomes of patients with breast cancer, working within the Cancer Intervention and Surveillance Modeling Network.[52,53] We then modified this model to simulate breast and ovarian cancer incidence, tumor characteristics, and prognosis under treatments recommended by practice guidelines (specific to tumor stage, size, and hormone receptors),[1,13,18,20,46,54-56] and the performance of screening mammography and MRI,[9,10,44,45] for *BRCA1/2* mutation carriers.[29,31] In sensitivity analyses, we varied parameters about which significant uncertainty exists, within CIs specified by published literature or more broadly (Table 1).

Patient Characteristics

The model simulates life histories of a 1980 birth cohort of 1,000,000 female *BRCA1/2* mutation carriers from age 25 years until age 100 years or death. We extrapolated *BRCA1/2*-associated cancer risks from meta-analyses.[1,2] Because approximately 30% of *BRCA1/2* mutation carriers undergo PO at a mean age of 45 years,[42,57,58] and because premenopausal PO reduces breast cancer incidence by approximately 50%,[4,5,40-42] we assumed that the incidence results from meta-analyses were affected by an unreported PO use of approximately 30%. To estimate breast cancer incidence in the absence of PO, we back-calculated the effect of a 50% reduction in subsequent breast cancer risk for 30% of the cohort as a result of PO performed by age 45 years.

Tumor Characteristics and Screen Detection

We assumed a tumor grade distribution for *BRCA1/2*-associated breast tumors consistent with published reports; estrogen receptor (ER) expression was modeled as a function of grade and mutation.[15,23] Tumor size and stage at clinical diagnosis were estimated as a function of grade, informed by the Surveillance Epidemiology and End Results (SEER) registry from the years before population-wide mammographic screening (1975 to 1981).[52,53] We assumed that *BRCA1/2*-associated breast and ovarian cancers are treated with standard therapies based on tumor size, stage, grade, ER expression, and other prognostic features and that treatment efficacy and prognosis equal those in the general population.[20,24,46,54,56,59,60] We assumed a median size detection threshold of 0.5 cm for MRI and that MRI has 85% sensitivity.[9,10,12,44] For mammography, we assumed a distribution of detection thresholds, with a median of 1 cm, and that a proportion of tumors are undetectable until they grow to 5 cm; we derived this proportion separately according to age and *BRCA* mutation, calibrating to published mammographic detection rates in this population (Table 1).[9,10,44,45]

Efficacy of Prophylactic Surgery

We assumed that PM reduces overall breast cancer incidence by 90%[18,19] and PO reduces annual ovarian cancer incidence by 80%.[5,6,42] We modeled the impact of PO as the annual probability of breast cancer detection at age i ($P_{i,PO}$) as $P_{i,PO} = P^{\alpha}_{i,NoPO}$, where $i \geq$ age at PO and α is the hazard ratio (HR). For ages less than 40 years, HR was 0.36, for ages 40 to 49 years, HR was 0.5, and

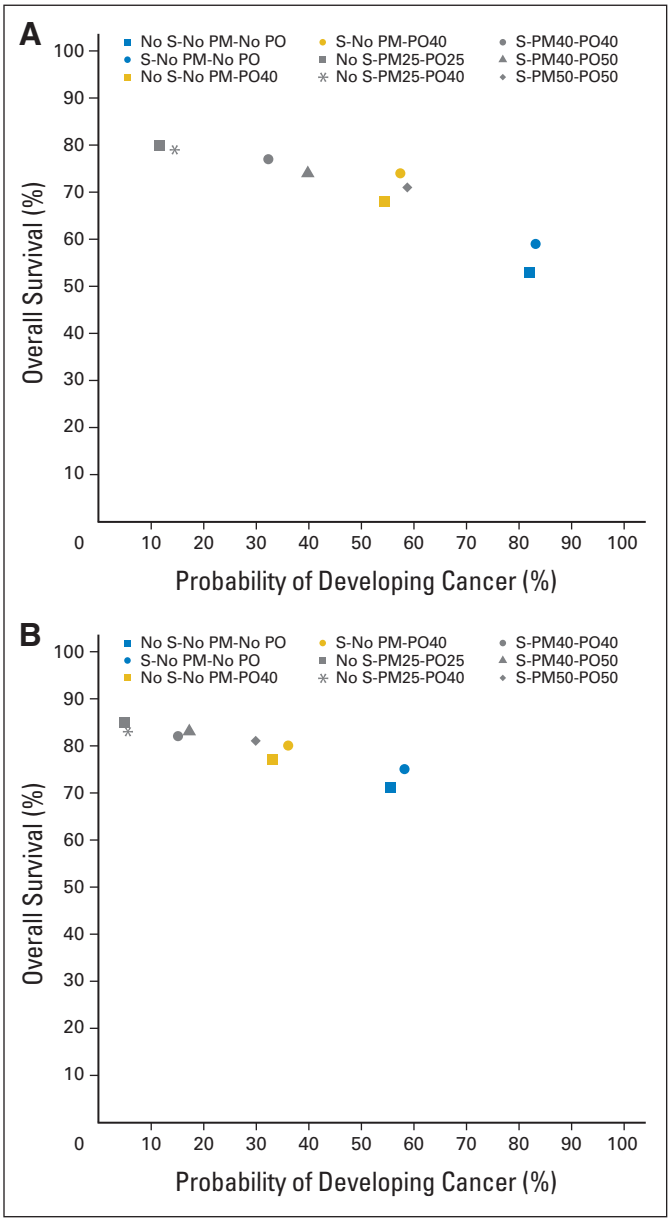

Fig 1. (A) Probability of developing cancer (combining breast and ovarian cancers) versus survival by age 70 years for *BRCA1* mutation carriers choosing different risk-reducing strategies, including prophylactic mastectomy (PM), prophylactic oophorectomy (PO), and/or annual breast screening (S) with mammography and magnetic resonance imaging, performed at various ages (age in years at time of surgery indicated by number after PM or PO). (B) Probability of developing cancer (combining breast and ovarian cancers) versus survival by age 70 years for *BRCA2* mutation carriers choosing different risk-reducing strategies, including PM, PO, and/or S, performed at various ages (age in years at time of surgery indicated by number after PM or PO).

for ages ≥ 50 years, HR was 1.0 (Table 1).[6,40] We assumed that the breast cancer risk reduction from PM at any age, and from PO before age 50 years, persists indefinitely.[41] We assumed that PO has no effect on breast cancer stage or ER expression.

Hormonal Exposures and Other-Cause Mortality

We did not explicitly model use of menopausal hormone therapy, oral contraceptive pills, or prophylactic tamoxifen or raloxifene, given uncertainty about their effects on cancer risks for *BRCA1/2* mutation carriers,[61-69] but we did explore their impact through sensitivity analyses of the effect of PO on breast cancer incidence. After PO performed at age less than 50 years, we conservatively assumed that cardiovascular disease doubles[47] and that osteoporotic hip fracture and dementia increase by 50%.[48-50] We computed other-cause mortality using the Berkeley Mortality database,[70] adjusting death rates from breast and ovarian cancer, cardiovascular disease, dementia, and hip fracture according to assumed relative risks (Table 1).[71,72] Previously, we found that reducing the incidence of cardiovascular disease, osteoporosis, and dementia (as would be anticipated with menopausal hormone therapy) had only a small (2% to 3%) impact on other-cause mortality,[29] so those sensitivity analyses were not repeated here.

Development of Online Decision Tool

We collaborated with software developers (L.C., P.R., M.S.) to build a model interface suitable for use as an online decision support tool. After obtaining human subjects approval from the Stanford University institutional review board and informed consent, we initiated pilot-testing of the tool with *BRCA1/2* mutation carriers accrued through the Stanford Clinical Cancer Genetics Program and the Facing Our Risk of Cancer Empowered advocacy group[73] and with clinicians from Stanford University Hospital and surrounding community practices.

RESULTS

Cancer Incidence Versus Survival in BRCA1/2 Mutation Carriers

In prior work, we reported survival with combinations of PM, PO, and screening[29]; we now expand our comparison of intervention strategies along the dual axes of incidence and survival. Figure 1 plots the probability of developing breast or ovarian cancer (combined) versus the probability of survival to age 70 years for *BRCA1*/2 mutation carriers. For *BRCA1* mutation carriers, survival is maximized (80%) and cancer incidence minimized (11%) by the combination of PM and PO (PM + PO) at age 25 years. By comparison, PM + PO at age 40 years yields 3% lower survival probability (77%) with a 21% increase in incidence (32%), whereas breast screening plus PO at age 40 years, without PM, yields 6% lower survival probability (74%) with a 46% increase in incidence (57%). For *BRCA2* mutation carriers,

Table 2. Breast and Ovarian Cancer Incidence at Specific Ages for *BRCA1/2* Mutation Carriers Under Risk-Reduction Strategies*

	No Breast Screening										Annual Breast Screening: Mammography and MRI									
	Cancer Incidence (%) at Specific Ages in Years																			
		PM Only			PO Only			PM + PO				PM Only			PO Only			PM + PO		
Mutation and Cancer Type	No PM or PO	At 25	At 40	At 50	At 25	At 40	At 50	At 25	At 40	At 50	No PM or PO	At 25	At 40	At 50	At 25	At 40	At 50	At 25	At 40	At 50
BRCA1 mutation carriers																				
Breast cancer incidence																				
Age 30 years	1	2	1	1	0	1	1	2	1	1	3	2	3	3	1	3	3	2	3	3
Age 40 years	12	3	12	12	5	12	12	2	12	12	17	3	17	17	7	17	17	2	17	17
Age 50 years	39	4	24	43	17	27	39	3	23	43	43	4	24	45	19	32	43	3	23	45
Age 60 years	56	6	25	47	27	39	56	3	24	47	59	6	25	47	29	43	59	3	24	47
Age 70 years	68	7	26	48	36	49	68	4	25	48	70	7	26	48	38	52	70	4	25	48
Age 80 years	78	8	27	49	45	58	78	5	25	49	78	8	27	49	45	60	78	5	25	49
Ovarian cancer incidence																				
Age 30 years	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Age 40 years	3	3	3	3	1	3	3	1	3	3	3	3	3	3	1	3	3	1	3	3
Age 50 years	13	13	13	13	3	5	13	3	5	13	13	13	13	13	3	5	13	3	5	13
Age 60 years	22	22	22	22	5	7	15	5	7	15	22	22	22	22	5	7	15	5	7	15
Age 70 years	38	38	38	38	8	10	18	8	10	18	38	38	38	38	8	10	18	8	10	18
Age 80 years	52	52	52	52	10	13	21	10	13	21	52	52	52	52	10	13	21	10	13	21
BRCA2 mutation carriers																				
Breast cancer incidence																				
Age 30 years	1	1	1	1	0	1	1	1	1	1	2	1	2	2	1	2	2	1	2	2
Age 40 years	6	2	6	6	2	6	6	2	6	6	9	2	9	9	4	9	9	2	9	9
Age 50 years	17	2	12	22	7	12	17	2	12	22	22	2	12	23	9	16	22	2	12	23
Age 60 years	34	4	13	26	14	21	34	2	12	26	38	4	13	26	16	25	38	2	12	26
Age 70 years	50	5	14	27	22	31	50	3	13	27	53	5	14	27	24	34	53	3	13	27
Age 80 years	63	6	15	28	30	41	63	3	14	28	63	6	15	28	30	42	63	3	14	28
Ovarian cancer incidence																				
Age 30 years	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Age 40 years	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Age 50 years	1	1	1	1	0	0	1	0	0	1	1	1	1	1	0	0	1	0	0	1
Age 60 years	7	7	7	7	2	2	3	2	2	3	7	7	7	7	2	2	3	2	2	3
Age 70 years	11	11	11	11	2	2	3	2	2	3	11	11	11	11	2	2	3	2	2	3
Age 80 years	15	15	15	15	3	3	4	3	3	4	15	15	15	15	3	3	4	3	3	4

Abbreviations: MRI, magnetic resonance imaging; PM, prophylactic mastectomy; PO, prophylactic oophorectomy.
*Risk-reduction strategies included PM or PO done at various ages, and breast screening with mammogram and MRI starting at age 25 years.

PM + PO at age 25 years maximizes survival (83%) and minimizes incidence (4%); by comparison, PM + PO at age 40 years reduces survival probability by 1% (82%), with an 11% increase in incidence (15%), whereas breast screening plus PO at age 40, without PM, yields 3% lower survival probability (80%) with a 22% increase in incidence (36%). For *BRCA1/2* mutation carriers, PM, PO, and PM + PO reduce breast cancer incidence, with a magnitude inversely related to age at surgery. The same is true for PO and ovarian cancer incidence, whereas screening slightly increases breast cancer incidence (Table 2). Results were most sensitive to assumptions about the efficacy of PO for breast cancer risk reduction and *BRCA1/2* mutation penetrance (Appendix Table A1, online only).

Breast Tumor Features and Treatments in BRCA1/2 *Mutation Carriers*

To characterize patients' treatment and survivorship experiences, we compared the outcomes of risk-reducing strategies in terms of breast tumor features at diagnosis: stage, size, ER expression, and recommended systemic treatments according to guidelines of the National Comprehensive Cancer Network.[54] Without risk-reducing interventions, *BRCA1* mutation carriers are most likely to develop an ER-negative tumor involving axillary lymph nodes (34%), corresponding to American Joint Committee on Cancer stage II to III[74]; next most likely diagnoses are a lymph node-negative, ER-negative tumor larger than 2 cm in size (mostly stage II; 16%) or a lymph node-positive, ER-positive tumor (stage II to III; 16%). These three most common scenarios require adjuvant chemotherapy; ER-positive tumors also require adjuvant hormonal therapy.[54] Adding MRI-based screening shifts the tumor stage and ER distribution: screened *BRCA1* mutation carriers have the greatest probability of a stage I, ER-negative tumor (42%, usually requiring chemotherapy), followed by a stage I ER-positive tumor (25%, requiring hormonal therapy and possibly chemotherapy) and a stage II to III, lymph node-positive, ER-negative tumor (14%, requiring chemotherapy; Table 3).[54]

Without intervention, *BRCA2* mutation carriers are most likely to develop a stage II to III, lymph node-positive, ER-positive tumor (36%, requiring chemotherapy and hormonal therapy), followed by a stage II, lymph node-negative, ER-positive tumor larger than 2 cm (20%, requiring hormonal therapy and probably chemotherapy) or a

Table 3. Stage and ER Expression (%) of BCs Diagnosed in *BRCA1/2* Mutation Carriers Under Risk Reduction With PM, PO, and/or Screening at Various Ages

	No Breast Screening										Annual Breast Screening: Mammography and MRI									
		PM Only			PO Only			PM + PO				PM Only			PO Only			PM + PO		
BC Stage and ER Expression (%)	No PM/PO	At 25	At 40	At 50	At 25	At 40	At 50	At 25	At 40	At 50	No PM/PO	At 25	At 40	At 50	At 25	At 40	At 50	At 25	At 40	At 50
BRCA1 mutation carriers																				
Local stage (lymph node negative)*																				
Tumor ≤ 2 cm (stage I)*																				
ER positive	8	21	19	11	8	8	8	25	19	11	25	21	29	28	24	25	25	25	30	28
ER negative	10	21	24	15	10	10	10	24	24	15	42	21	43	45	39	40	41	24	44	45
Tumor > 2 cm (majority stage II)*																				
ER positive	9	6	5	8	9	9	9	5	5	8	3	6	2	3	4	4	3	5	2	3
ER negative	16	10	10	14	16	16	16	8	10	14	8	10	6	7	9	8	8	8	5	7
Regional stage (lymph node positive, stage II-III)*																				
ER positive	16	12	12	14	16	16	16	11	12	14	5	12	5	5	6	6	5	11	5	5
ER negative	34	25	25	31	34	34	34	22	25	31	14	25	13	12	16	15	15	22	12	12
Distant stage (metastatic, stage IV)*																				
ER positive	2	1	1	2	2	2	2	1	1	2	0	1	0	0	1	0	0	1	0	0
ER negative	6	4	4	6	6	6	6	3	4	6	1	4	1	1	2	2	1	3	1	1
BRCA2 mutation carriers																				
Local stage (lymph node negative)*																				
Tumor ≤ 2 cm (stage I)*																				
ER positive	18	37	38	33	18	18	18	46	40	33	55	37	59	63	52	54	54	46	62	63
ER negative	4	6	7	6	4	4	4	8	7	6	13	6	13	14	12	13	13	8	13	14
Tumor > 2 cm (majority stage II)*																				
ER positive	20	14	13	15	20	20	20	10	12	15	9	14	7	6	10	9	9	10	6	6
ER negative	5	4	3	4	5	5	5	3	3	4	3	4	2	2	3	3	3	3	2	2
Regional stage (lymph node positive, stage II-III)*																				
ER positive	36	27	26	29	36	36	36	22	25	29	14	27	13	10	15	14	14	22	12	10
ER negative	11	8	8	9	11	11	11	7	8	9	5	8	4	4	5	5	5	7	4	4
Distant stage (metastatic, stage IV)*																				
ER positive	5	3	3	4	5	5	5	3	3	4	1	3	1	1	1	1	1	3	1	1
ER negative	2	1	1	1	2	2	2	1	1	1	1	1	0	0	1	1	1	1	0	0

Abbreviations: BC, breast cancer; ER, estrogen receptor; MRI, magnetic resonance imaging; PM, prophylactic mastectomy; PO, prophylactic oophorectomy; SEER, Surveillance, Epidemiology, and End Results.

*Given use of data from the SEER registry to develop the model, SEER tumor stages are reported (local, regional distant, as described in Table 1); corresponding stages of the American Joint Committee on Cancer[74] are presented in parentheses.

stage I, lymph node-negative, ER-positive tumor (18%, requiring hormonal therapy and possibly chemotherapy; Table 3).[54] With MRI-based screening, *BRCA2* mutation carriers are most likely to have a stage I, ER-positive cancer (55%, requiring hormonal therapy and possibly chemotherapy), followed by a stage II to III lymph node-positive, ER-positive tumor (14%, requiring chemotherapy and hormonal therapy), and a stage I, ER-negative tumor (13%, usually requiring chemotherapy).[54] Results were most affected by our assumptions about the sensitivity of screening MRI (Appendix Table A1). Figure 2 presents risks of developing breast cancer to age 70 years, stratified by likely systemic treatments,[54] for *BRCA1/2* mutation carriers under various strategies.

Model Runs Underlying the Online Decision Tool

To inform an age- and mutation-specific decision tool, we performed 2,130 model runs, considering cancer-free women with *BRCA1* and *BRCA2* mutations, in the age intervals of 25 to 29, 30 to 34, 35 to 39, 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, and 65 to 69 years. Because each run simulates the individual histories of 1,000,000 women, our estimates incorporate outcomes of more than 1,000,000,000 women, stratified by age at *BRCA1/2* mutation testing and risk-reducing intervention. Results of all runs are presented in the online decision tool.

Development and Features of the Online Decision Tool

We developed an online user interface with a vertical bar-graph display, adapting figures from our prior survival analysis[29] and from our current work on cancer incidence, features, and treatments (Fig 2). We selected a bar-graph format by analogy to the successful Adjuvant! model for breast cancer treatment.[75,76] User-selected variables are patient characteristics (age and mutation) and intervention strategies (annual screening mammogram, annual screening MRI, PM, and PO, alone or in combination at different ages). Each vertical bar represents a selected strategy showing the following outcomes: survival probability to age 70 years, causes of death, breast and ovarian cancer incidence, and breast tumor features influencing treatment recommendations (stage and hormone receptor expression). Of six vertical bars, the middle four can be customized to report specific strategies; for comparison, the left-most anchoring bar shows outcomes if no risk-reducing interventions are undertaken and the right-most anchoring bar shows the outcomes of an age-matched woman with no *BRCA1/2* mutation. The four user-customized bars can be ranked by survival, and the display can be printed. Figure 3 presents the main screen of the tool; the user can choose to display survival and causes of death only (Fig 3A) or to include features and guideline-recommended treatments of breast cancers (Fig 3B). Additional screens include (1) an introduction, specifying the intended use conditions under physician supervision, the intended population, and the modeling assumptions; (2) a glossary; (3) contact information; and (4) publication links. The decision tool is available online.[77]

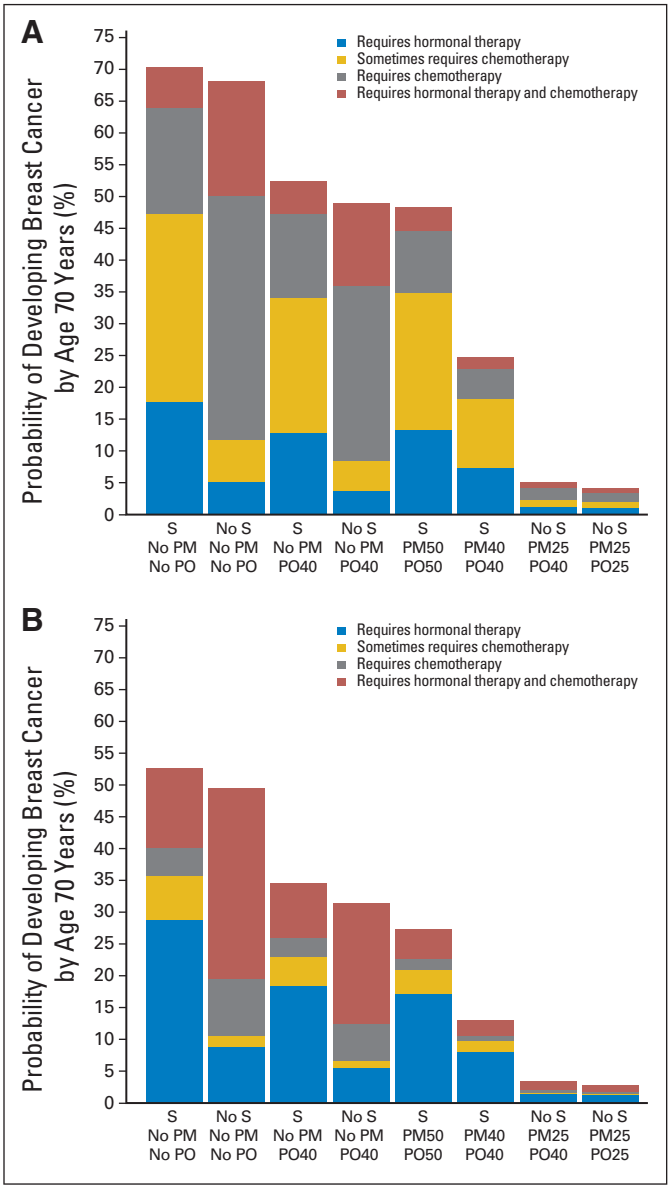

Fig 2. (A) Absolute risk of developing breast cancer by age 70 years, stratified by guideline-recommended systemic treatments according to stage, size, and estrogen receptor expression, for *BRCA1* mutation carriers who choose risk-reducing strategies including annual breast screening (S) with mammography and magnetic resonance imaging, prophylactic mastectomy (PM), and/or prophylactic oophorectomy (PO) performed at various ages (age in years indicated by number after PM or PO). (B) Absolute risk of developing breast cancer by age 70 years, stratified by guideline-recommended systemic treatments according to stage, size, and estrogen receptor expression, for *BRCA2* mutation carriers who choose risk-reducing strategies including S, PM, and/or PO performed at various ages (age in years indicated by number after PM or PO).

DISCUSSION

We built a simulation model to estimate and compare multiple health outcomes for *BRCA1/2* mutation carriers under various cancer risk-reduction strategies and converted it into an online decision tool for use by physicians and patients. We found that early prophylactic mastectomy and salpingo-oophorectomy most effectively prevent cancer, but alternatives that reduce cancer incidence far less substantially can offer comparable survival. MRI-based breast screening yields this benefit through a diagnostic stage shift, increasing the proportion of stage I tumors from 18% to 22% up to 67% to 68%; treatment recommendations vary by hormone receptor expression, which is correlated with the type of *BRCA* mutation. A *BRCA2* mutation carrier who elects MRI screening may well escape a recommendation for adjuvant chemotherapy, because 81% of

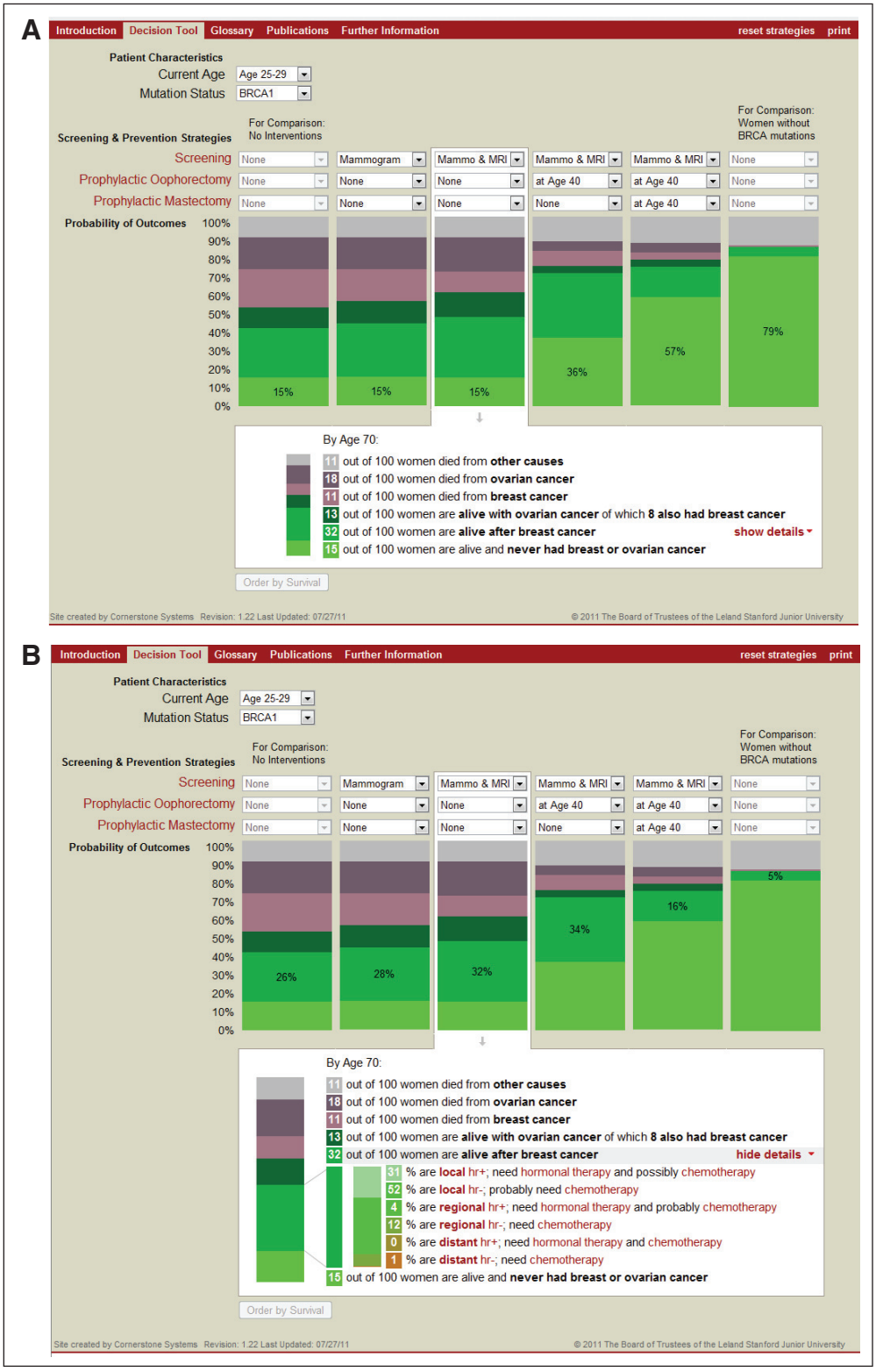

Fig 3. (A) Display screen of online decision tool (brcatool.stanford.edu) comparing user-selected scenarios for cancer risk reduction. Screening options include yearly mammography (Mammo) and/or magnetic resonance imaging (MRI); preventive options include prophylactic mastectomy or salpingo-oophorectomy at various ages. Each bar shows the probability of outcomes by age 70 years under the selected strategy in terms of cancer-free survival (light green), survival after breast cancer (darker green), survival with ovarian cancer (darkest green), and death resulting from breast cancer (pink), ovarian cancer (purple), and other causes (gray). Terms in red font are linked to definitions in the glossary. (B) Expanded display screen of decision tool, showing additional details of each user-selected scenario (vertical bars) in terms of breast cancer stage (local, regional, distant), hormone receptor (hr) expression (negative – or positive +), and recommended systemic therapies according to practice guidelines.

breast cancers diagnosed in this setting are smaller than 2 cm, node-negative, and hormone receptor-positive. The online decision tool[77] enables direct comparison of many possible strategies for an individual patient, combining various screening methods with prophylactic surgeries undertaken at different ages and weighing their impact on cancer incidence, treatment experiences, and survival.

Decisions about cancer risk reduction are complex and highly personal. For most women in the population, the greatest challenge is

estimating risk accurately.[78] Imprecision in communicating risk-benefit ratios may contribute to under-utilization of effective strategies such as chemoprevention.[79] For *BRCA1/2* mutation carriers, cancer risks are higher and better defined, driving greater uptake of prophylactic surgeries and intensive surveillance.[57,58] Nonetheless, a significant number of women with *BRCA1/2* mutations never develop cancer, given variations in penetrance which are incompletely understood[80-82]; removing organs at risk thus remains a gamble. Use of prophylactic surgeries varies by country, age, and prior cancer diagnosis, and aspects of personal experience such as family cancer history and parity play a role.[56,57,83,84] Prior decision analyses have assigned a set value to life after prophylactic surgery or with screening and reported results in quality-adjusted life years.[25,27,31,85,86] Given our experience of substantial variation in patient preferences, we elected against ranking health states under different risk-reducing interventions. Instead, our estimates across multiple outcomes aim to guide patients in optimizing their quality of life, depending on their individual values: for one woman this could entail retaining her breasts for decades, with eventual diagnosis of an early-stage breast cancer that might require chemotherapy; for another, this could entail maximal cancer prevention by removing her breasts and ovaries early in life.

With rapid growth in therapeutic and diagnostic technology, decision aids are increasingly used in oncology practice. They synthesize diverse data sources and integrate comparisons across disparate (and often conflicting) scales of benefit, such as efficacy, toxicity, and cost. Trials have demonstrated improvements in decisional conflict and satisfaction with the use of decision aids in breast, colorectal, and thoracic oncology.[76,87-92] Decision aids weigh the absolute magnitude of an intervention's benefit against competing risks and may align choices more closely with expected therapeutic gains.[93] The online format of our decision tool facilitates access and personalization; results are customized for a patient's age, allowing women to revisit their decisions over time should their health status, life circumstances, or priorities change. Additionally, the online tool can be readily adapted to accommodate new data from emerging studies. No decision aid can replace any aspect of the physician–patient relationship; our tool aims rather to channel the discussion toward choices that more fully realize a patient's personal preferences.

Our work has some limitations. The results of any simulation model depend on its assumptions. We initially developed and validated our model with SEER registry data, modeling tumor growth and ER expression as a function of grade[52,53,94]; we subsequently applied this same strategy to *BRCA1/2*-associated breast cancers, using appropriate tumor grade and ER distributions.[13,15,23,55,95,96] Although justified by reports that patients with breast cancer with and without *BRCA1/2* mutations have similar outcomes,[20,59,60,97] this fundamental approach is difficult to validate. The model lacks data on breast tumor progesterone receptor and human epidermal growth factor receptor 2 expression, given their absence in SEER; because human epidermal growth factor receptor 2 overexpression is rare in *BRCA1/2* -associated tumors,[13,55,95,96] this limitation is unlikely to change our conclusions. An additional limitation is our use of average *BRCA1/2* mutation penetrance estimates, derived from meta-analyses[1,2]; our model does not incorporate factors that may mediate individual risk variation, such as birth cohort, family history, lifestyle and environmental exposures, or single-nucleotide polymorphisms in other genes.[81,82,98,99] We did not assign a separate prognostic category to carcinoma in situ or consider emerging treatments such as poly (ADP-ribose) polymerase inhibitors. We varied input parameters widely in sensitivity analyses and found that our assumptions about *BRCA1/2*-associated cancer risks, the sensitivity of MRI, and the effect of PO on breast cancer incidence were most influential. If MRI-based breast screening detects preinvasive cancers,[9,45,100] which have optimal survival and no requirement for chemotherapy,[74] or if *BRCA1/2* mutation-targeted cancer therapies improve survival with few adverse effects,[101-104] then breast screening may provide a better outcome than we estimate; conversely, if mutation penetrance is higher or cancer prognosis worse than we estimate, prophylactic surgeries would appear more favorable. The online decision tool focuses on cancer-free women; it does not report second primary cancer risks, mortality from a prior cancer, or benefit from a procedure performed in the past. We have not measured the tool's impact on decision outcomes in a clinical trial, but pilot-testing among 60 patients and providers yielded high rankings on clinical relevance and ease of use, with a full analysis underway. Future work is warranted to address these limitations of the model and decision tool.

We calculated cancer incidence, tumor prognostic features that influence treatment and quality of life, overall survival, and cause-specific mortality under many possible risk-reduction strategies for *BRCA1/2* mutation carriers. We customized these results by age and *BRCA* mutation and adapted them into an online tool to support joint decision making by patients and physicians. By characterizing the multiple health outcomes associated with cancer risk-reduction options, our decision tool aims to clarify a patient's priorities and guide choices that preserve them.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Allison W. Kurian, Lauren Clarke, Sylvia K. Plevritis
Financial support: Allison W. Kurian, Sylvia K. Plevritis
Provision of study materials or patients: Allison W. Kurian, Elizabeth A. Schackmann, Sylvia K. Plevritis
Collection and assembly of data: All authors
Data analysis and interpretation: Allison W. Kurian, Diego F. Munoz, Elizabeth A. Schackmann, Meredith A. Mills, Sylvia K. Plevritis
Manuscript writing: All authors
Final approval of manuscript: All authors

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