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ORIGINAL REPORT

Survival Analysis of Cancer Risk Reduction Strategies for *BRCA1/2* Mutation Carriers

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ABSTRACT

Purpose
Women with *BRCA1/2* mutations inherit high risks of breast and ovarian cancer; options to reduce cancer mortality include prophylactic surgery or breast screening, but their efficacy has never been empirically compared. We used decision analysis to simulate risk-reducing strategies in *BRCA1/2* mutation carriers and to compare resulting survival probability and causes of death.

Methods
We developed a Monte Carlo model of breast screening with annual mammography plus magnetic resonance imaging (MRI) from ages 25 to 69 years, prophylactic mastectomy (PM) at various ages, and/or prophylactic oophorectomy (PO) at ages 40 or 50 years in 25-year-old *BRCA1/2* mutation carriers.

Results
With no intervention, survival probability by age 70 is 53% for *BRCA1* and 71% for *BRCA2* mutation carriers. The most effective single intervention for *BRCA1* mutation carriers is PO at age 40, yielding a 15% absolute survival gain; for *BRCA2* mutation carriers, the most effective single intervention is PM, yielding a 7% survival gain if performed at age 40 years. The combination of PM and PO at age 40 improves survival more than any single intervention, yielding 24% survival gain for *BRCA1* and 11% for *BRCA2* mutation carriers. PM at age 25 instead of age 40 offers minimal incremental benefit (1% to 2%); substituting screening for PM yields a similarly minimal decrement in survival (2% to 3%).

Conclusion
Although PM at age 25 plus PO at age 40 years maximizes survival probability, substituting mammography plus MRI screening for PM seems to offer comparable survival. These results may guide women with *BRCA1/2* mutations in their choices between prophylactic surgery and breast screening.

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INTRODUCTION

More than 300,000 women in the United States are estimated to carry a mutation in the *BRCA1* or *BRCA2* genes[1]; with these mutations, women inherit 5- to 20-fold increased risks of developing breast and ovarian cancer.[2] Cancer risk management strategies for *BRCA1/2* mutation carriers incorporate earlier, more frequent, and more invasive intervention than those for the general population. Practice guidelines recommend prophylactic bilateral salpingo-oophorectomy (PO) for ovarian cancer risk reduction by age 40 years (all ages are given in years hereafter) and support various alternatives for managing breast cancer risk: either prevention with prophylactic mastectomy (PM) or early detection with screening mammography plus breast magnetic resonance imaging (MRI).[3,4]

Although studies in *BRCA1/2* mutation carriers have reported efficacy of PO and PM for cancer prevention[5-9] and of mammography plus MRI screening for early breast cancer detection,[10-13] most were limited in size, and none directly compared survival after screening versus surgery. Moreover, all risk-reducing options have disadvantages. PM and premenopausal PO are permanent procedures that limit reproductive choices; PM can impair body image, and PO may impose health risks of early menopause.[14-18] Screening MRI yields frequent false positives, thereby increasing anxiety and costs.[19] To the best of our knowledge, no randomized trial is planned to compare survival benefit and other health outcomes from different strategies aimed at reducing cancer mortality in *BRCA1/2* mutation carriers. Moreover, patients may not accept random assignment between prophylactic surgery and

screening, and many clinicians question the ethics of asking them to do so. Therefore, women and their physicians must navigate among disparate and invasive alternatives with little empiric guidance when choosing how best to manage cancer risks. To optimally inform such decisions, we developed a simulation modeling approach to compare the survival probability for *BRCA1/2* mutation carriers after several risk-reduction strategies, based on the best available evidence. This approach builds on our prior evaluation of the cost-effectiveness of MRI screening in *BRCA1/2* mutation carriers[19] and additionally considers PO and PM as alternatives or complements to MRI-based breast screening. We now report survival probability with various clinically relevant risk-reducing strategies for women with *BRCA1/2* mutations, aiming to target survival estimates to individual patients and enable personalized cancer risk management.

METHODS

We used a computer simulation model that integrates empiric data from the literature (Table 1) to estimate survival probability and causes of death at ages 70 and 80 years for 25-year-old women with a *BRCA1* or *BRCA2* mutation. Risk-reducing interventions were modeled alone and in combination, at ages specified by cancer care guidelines[3,4]: breast screening with mammography plus MRI started at age 25 and continued annually to age 69, PO was performed at age 40 or 50, and PM was evaluated for ages 25 to 50 years.

Overview of Computer Simulation Model

We previously developed a Monte Carlo simulation model to analyze the impact of screening and treatment on outcomes of individual breast cancer patients.[42,43] We then modified the model to incorporate breast and ovarian cancer incidence, tumor characteristics, prognosis under standard treatments,[2,24,37,39,44-47] and the performance of screening with mammography and MRI[10-13] in *BRCA1/2* mutation carriers.[19] For this study, we added literature-based estimates of the effects of PM and PO on survival probability and causes of death (Table 1).

Patient Characteristics

The model simulates the life histories of a 1980 birth cohort of 1,000,000 female *BRCA1* or *BRCA2* mutation carriers from age 25 until age 100 or death, whichever occurs first. We extrapolated cancer risks for *BRCA1* and *BRCA2* mutation carriers from meta-analyses.[2,20] Since approximately 30% of *BRCA1/2* mutation carriers undergo PO at a mean age of 45,[7] we assumed that reported breast cancer incidence[2] incorporates 30% use of PO. We adjusted our estimates of breast cancer risk without PO, given that PO in premenopausal *BRCA1/2* mutation carriers reduces breast cancer risk by approximately 50%.[6-8,25] We assumed that *BRCA1/2* mutation carriers receive standard breast and ovarian cancer therapies and that treatment efficacy and cancer prognosis equal those of the general population[39,45-48] (Table 1).

Efficacy of Prophylactic Surgery

We assumed that PM reduces breast cancer risk by 90%.[9,24] We assumed that PO reduces ovarian cancer risk by 85%[7,8] and breast cancer risk by 50% when performed between ages 40 and 50, with no impact on breast cancer risk when performed at or after age 50 (Table 1).[6,49] We assumed that the breast cancer risk reduction after premenopausal oophorectomy persists indefinitely.[25]

Other-Cause Mortality After Premenopausal PO

We assumed no use of menopausal hormone therapy, given uncertainty about its effect on breast cancer in *BRCA1/2* mutation carriers.[50-52] After PO before age 50,[3] we assumed a two-fold increased risk of cardiovascular disease[40] and a 50% increased risk of osteoporotic hip fracture and dementia[16,17,41]; as have previous studies,[53,54] we assumed these increases would last until age 65. To compute other-cause mortality, we adjusted data from the Berkeley Mortality Database 1980 birth cohort table[55] by removing breast and ovarian cancer deaths based on 2004 US rates reported by the Centers for Disease Control and Prevention (diagnostic codes C50 and C56)[56] and adjusting mortality rates from cardiovascular disease, dementia, and hip fracture (codes I20-I25, F0, F3, G20-G21, and G30)[54,56] according to the assumed relative risks (Table 1).

Sensitivity Analyses

We varied model parameters about which significant uncertainty exists: risk of developing breast and ovarian cancer with a *BRCA1* or *BRCA2* mutation, breast tumor volume doubling time (TVDT), sensitivity of MRI for cancer detection, impact of oral contraceptive pills on breast and ovarian cancer risk, and impact of premenopausal PO on breast cancer and other-cause mortality (Table 1).[2,6,8,17,20-23, 26-36,38,49] Sensitivity analyses considered four clinically relevant scenarios: no intervention, mammography plus MRI screening without surgery, screening plus PO at age 40, and screening plus PO and PM at age 40.

RESULTS

Cancer Risk by Age 70 in BRCA1 Mutation Carriers

In the absence of breast screening, PM at age 40 reduces breast cancer risk to 27%; PO at age 40 reduces breast cancer risk to 49% and ovarian cancer risk to 9%. Performing PM and PO at age 40 reduces breast cancer risk to 25% and ovarian cancer risk to 9%. Screening has no impact on ovarian cancer risk and minimal impact on breast cancer risk (data not shown).

Overall Survival in BRCA1 Mutation Carriers

With no intervention, survival probability by age 70 years is 53% for *BRCA1* mutation carriers versus 84% for the general US population (Table 2). The most effective single intervention is PO at age 40, yielding a survival probability of 68% by age 70, which represents a 15% absolute gain compared with no intervention (68% *v* 53%). Delaying PO to age 50 yields half the survival gain provided by PO at age 40 (8%: 61% *v* 53% with no intervention). In comparison, PM at age 25 yields a 13% gain relative to no intervention, whereas delaying PM to age 40 yields a small (2%) decrement in gain compared with PM at age 25. Breast screening alone from ages 25 to 69 yields the lowest gain (6%).

The most effective combination strategy is PM at age 25 plus PO at age 40, providing a 26% survival gain by age 70 compared with no intervention (79% *v* 53%). Postponing PM until age 40, in the presence of screening from ages 25 to 39 and PO at age 40, reduces survival gain by 2%. Eliminating PM and substituting breast screening from ages 25 to 69 while performing PO at age 40 reduces survival gain by an incremental 3%. When added to PO at age 40, breast screening offers 5% lower survival probability than does PM at age 25 (74% *v* 79%) and 3% lower survival probability than does PM at age 40 (74% *v* 77%). If PO is delayed until age 50, breast screening offers 5% lower survival probability than PM at age 40 (69% *v* 74%). Results by age 80 are similar (Table 2). Figure 1A presents survival probability, and Figure 2A presents distribution of health status by age 70 years in *BRCA1* mutation carriers under various intervention scenarios.

Cause-Specific Mortality in BRCA1 Mutation Carriers

Among *BRCA1* mutation carriers who choose no intervention, the likelihood of death from breast versus ovarian cancer is similar (41% *v* 36%, conditional on death by age 70; Table 2). With PO at age

Table 1. Tumor, Screening, and Intervention Characteristics

Characteristic	Base Case Values		Range for Analyses	Source
	BRCA1	*BRCA2*		
Breast cancer risk and RR				
Cumulative breast cancer risk by age 70 years[a]	0.65	0.45	0.47-0.85 (*BRCA1*) 0.4-0.85 (*BRCA2*)	Antoniou et al,[2] Chen et al,[20] Evans et al,[21] Ford et al,[22] King et al[23]
Ten-year risk of second primary breast tumor	0.43	0.35	Not varied	Metcalfe et al[24]
RR for breast cancer with PM[b]	0.9	0.9	Age 25-50	Rebbeck et al[9]
RR for breast cancer with PO, by age (years) at PO[c]			0-0.9 for ages 40-50[c]	Eisen et al,[6] Kramer et al[25]
40-50	0.50	0.50		
≥ 50	None	None		
Duration of RR for breast cancer after PO	Lifelong	Lifelong	Not varied	Eisen et al,[6] Kramer et al[25]
Ovarian cancer risk and RR				
Cumulative ovarian cancer risk by age 70 years	0.39	0.11	0.39-0.46 (*BRCA1*) 0.11-0.27 (*BRCA2*)	Antoniou et al,[2] Chen et al,[20] Evans et al,[21] Ford et al,[22] King et al[23]
RR for ovarian cancer from PO	0.85	0.85	Not varied	Finch et al[7]
Oral contraceptives, when used for at least 5 years	No use	No use	HR for ovarian cancer, 0.5 HR for breast cancer, 0-1.5	Brohet et al,[26] Haile et al,[27] Jernström et al, [28] Lee et al,[29] McGuire et al,[30] McLaughlin et al,[31] Milne et al,[32] Modan et al,[33] Narod et al,[34] Narod et al,[35] Whittemore et al[36]
Breast cancer characteristics at symptomatic detection (no screening)				
Distribution of tumor grade				
I-II	0.29	0.57	Not varied	Chappuis et al[37]
III	0.71	0.43		
Distribution of ER positivity, by age in years				
20-49	0.18	0.62	Not varied	Chappuis et al[37]
50-69	0.22	0.75		
≥ 70	0.24	0.83		
Distribution of tumor size, cm				
< 2	0.29	0.33	Not varied	Estimated[d]
2-5	0.55	0.54		
> 5	0.16	0.13		
Distribution of tumor stage				
Local	0.43	0.47	Not varied	Estimated[d]
Regional	0.49	0.46		
Distant	0.08	0.07		
Mean tumor volume doubling time,[e] months	5.7	6.8	0.5-12	Tilanus-Linthorst et al[38]
Screening test and protocol characteristics				
Screening interval, years	1	1	Not varied	Assumed
Age of annual mammography screening, years	25-69	25-69	Not varied	Assumed
Age of annual MRI screening, years	25-69	25-69	Not varied	Assumed
Sensitivity of MRI screening for cancer detection,[f] %	85	85	50, 90	Kriege et al,[10] Kuhl et al,[11] Leach et al,[12] Warner et al[13]
MRI tumor size detection threshold, cm	0.5	0.5	0.3, 1.53[f]	Plevritis et al[19]
Mammography median tumor size detection threshold,[g] cm	1	1	Not varied	Plevritis et al[19]
Proportion of tumors undetectable by mammography by age, years				
< 50	0.66	0.66	Not varied	Estimated[h]
≥ 50	0.3	0.3		
Relative risk for breast cancer death after adjuvant systemic therapy				
Adjuvant multi-agent chemotherapy by age, years				
< 50	0.47	0.47	Not varied	Early Breast Cancer Trialists' Collaborative Group[39]
≥ 50	0.31	0.31		
Adjuvant tamoxifen for ER-positive breast cancers	0.31	0.31	Not varied	Early Breast Cancer Trialists' Collaborative Group[39]
Relative risk for other-cause mortality after PO				
Death from cardiovascular disease	2.0	2.0	0.5-2.5	Colditz et al[40]
Death related to hip fracture	1.5	1.5	1.0-2.0	Melton et al[41]
Death related to dementia	1.5	1.5	0.5-2.0	Rocca et al,[16] Rocca et al,[17] Melton et al[41]

Abbreviations: RR, risk reduction; PM, prophylactic mastectomy; PO, prophylactic oophorectomy; HR, hazard ratio; ER, estrogen receptor; MRI, magnetic resonance imaging.

[a]Reported lifetime breast cancer risks were assumed to have incorporated a 30% background rate of PO at age 45 years[7]; time to second breast cancer was modeled with a Weibull distribution.

[b]We assumed that the reduction in the probability of developing breast cancer after PM was 0.95 (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 (90% reduction).[24]

[c]In the base case, we assumed an HR of 0.5 (proportional hazard reduction of 50%) for subsequent breast cancer in women undergoing PO between ages 40 and 50.[6] In sensitivity analyses, we evaluated the assumptions that PO had no effect on subsequent breast cancer risk (HR, 1.0 for women of all ages) and that PO conveyed an HR of 0.1 for all women undergoing the procedure before age 50 (proportional hazard reduction of 90%). We assumed no reduction in the HR of breast cancer for women undergoing PO at or after age 50.

[d]Derived from our breast cancer natural history model using SEER data from 1975 to 1981.

[e]The mean tumor volume doubling time was estimated by calibrating to approximately 85% sensitivity of screening breast MRI in the population with *BRCA1* mutations,[10-13] on the basis of the condition that the mean tumor volume doubling time of grade III tumors is approximately 0.54 times the mean tumor volume doubling time of grade I-II tumors, which we derived analytically.

[f]MRI sensitivity was varied in sensitivity analysis by adjusting the tumor size detection threshold between 0.3 cm (90% sensitivity) and 1.53 cm (50% sensitivity).

[g]The median mammography threshold applies only among women whose tumor is detectable by mammography.

[h]Estimated by calibrating to mammographic screening sensitivity, which was assumed to be 0.25 under age 50,[12] and 0.5 at age ≥ 50. Tumors ≥ 5 cm were assumed to always be detectable by mammography.

Table 2. Probability of OS, BCD, OCD, and OD by Ages 70 and 80 in 25-Year-Old Women With *BRCA1/2* Mutations

Variable	Survival by Age 70, With No PO				Survival by Age 70, With PO at Age 40				Survival by Age 70, With PO at Age 50			
	OS	BCD*	OCD*	OD*†	OS	BCD*	OCD*	OD*†	OS	BCD*	OCD*	OD*†
BRCA1 mutation carriers												
No screening, no PM	53	41	36	23	68	45	12	43	61	51	20	29
Screening, no PM	59	26	46	28	74	30	15	55	69	34	26	40
Screening, PM age 50	61	21	48	31	75	25	17	58	71	28	28	44
Screening, PM age 40	64	13	53	34	77	18	18	64	74	18	32	50
Screening, PM age 30	66	6	57	37	79	8	20	72	76	9	36	55
No screening, PM age 25	66	5	58	37	79	6	21	73	76	7	36	57
BRCA2 mutation carriers												
No screening, no PM	71	36	20	44	77	30	4	66	75	42	6	52
Screening, no PM	75	21	25	54	80	18	5	77	79	26	8	66
Screening, PM age 50	77	15	27	58	81	13	5	82	81	18	8	74
Screening, PM age 40	78	9	28	63	82	9	6	85	83	11	9	80
Screening, PM age 30	79	5	30	65	83	4	6	90	83	6	10	84
No screening, PM age 25	79	4	30	66	83	3	6	91	83	5	10	85
General US female population	84	8	3	89	Not applicable				Not applicable			
	Survival by Age 80, With No PO				Survival by Age 80, With PO at Age 40				Survival by Age 80, With PO at Age 50			
BRCA1 mutation carriers												
No screening, no PM	33	33	36	31	50	35	11	54	44	42	17	41
Screening, no PM	38	21	43	36	55	23	13	64	51	27	20	53
Screening, PM age 50	41	14	46	40	58	15	15	70	54	19	22	59
Screening, PM age 40	43	9	49	42	59	11	15	74	57	12	24	64
Screening, PM age 30	44	4	51	45	61	5	16	79	59	6	25	69
No screening, PM age 25	44	4	52	44	61	4	16	80	59	5	26	69
BRCA2 mutation carriers												
No screening, no PM	52	29	16	55	59	22	3	75	56	32	4	64
Screening, no PM	56	17	19	64	62	13	4	83	61	20	5	75
Screening, PM age 50	59	9	21	70	64	7	4	89	64	11	5	84
Screening, PM age 40	60	6	21	73	65	5	4	91	65	6	6	88
Screening, PM age 30	61	3	22	75	65	3	4	93	66	4	6	90
No screening, PM age 25	61	3	22	75	65	2	4	94	66	3	6	91
General US female population	66	6	2	92	Not applicable				Not applicable			

NOTE. Interventions include screening, PM at various ages, and PO at ages 40 and 50. Screening consists of mammography and magnetic resonance imaging annually[3,4]; it is initiated at age 25 and continued through age 69 unless PM occurs.

Abbreviations: OS, overall survival; BCD, breast cancer death; OCD, ovarian cancer death; OD, other-cause death; PO, prophylactic oophorectomy; PM, prophylactic mastectomy.

*Probability of death as a result of breast cancer, ovarian cancer, or other causes given death by age 70 or 80, expressed as a percent.

†Other-cause mortality from the Berkeley Tables[55] was corrected by removing BCDs and OCDs, as reported by the Centers for Disease Control and Prevention in 2004.[56]

40 only, death from ovarian cancer decreases dramatically, making breast cancer deaths most frequent (45%, followed by other-cause [43%] and ovarian cancer deaths [12%]). When PO is delayed from age 40 to age 50, ovarian cancer deaths nearly double; breast cancer deaths increase less markedly. Among women who choose breast screening until age 40 and then PO plus PM at age 40, 23% will die by age 70; most (64%) die of non-cancer causes, followed by breast cancer (18%) and ovarian cancer (18%). Results are comparable for women who choose breast screening until age 69 and then PO at age 40, but not PM, and follow a similar pattern by age 80 (Table 2).

Cancer Risk by Age 70 in BRCA2 *Mutation Carriers*

In the absence of breast screening, PM at age 40 reduces breast cancer risk to 14%; PO at age 40 reduces breast cancer risk to 31% and ovarian cancer risk to 2%. Performing PM and PO at age 40 reduces breast cancer risk to 13% and ovarian cancer risk to 2%. Screening has no impact on ovarian cancer risk and minimal impact on breast cancer risk (results not shown).

Overall Survival in BRCA2 *Mutation Carriers*

With no intervention, survival probability by age 70 is 71% for *BRCA2* mutation carriers versus 84% for the general population (Table 2). The most effective single intervention is PM at age 25, yielding an 8% gain compared with no intervention (79% *v* 71%); postponing PM to age 40 reduces gain by 1%. In comparison, PO at age 40 yields a 6% gain relative to no intervention, and breast screening alone, with annual MRI plus mammography, provides a 4% gain. Delaying PO from age 40 to age 50 reduces gain by 2%.

The most effective combination strategy is PM at age 25 plus PO at age 40, providing a 12% survival gain by age 70 compared with no intervention (83% *v* 71%). Postponing PM until age 40 in the presence of breast screening from ages 25 to 39 and PO at age 40 reduces

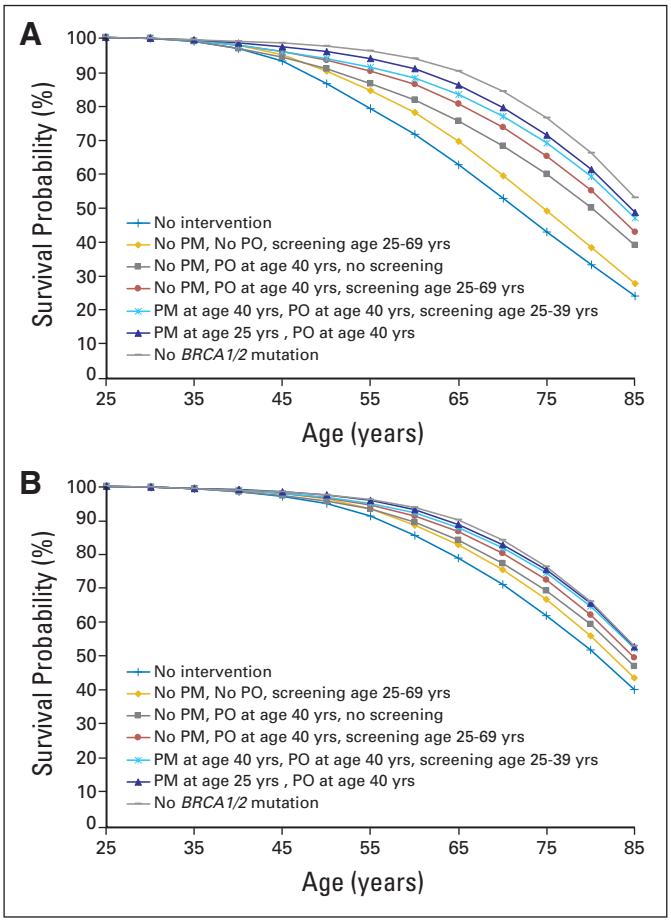

Fig 1. Survival probability after different risk-reducing strategies, including no intervention, screening with mammography plus magnetic resonance imaging (screening), prophylactic mastectomy (PM), and prophylactic oophorectomy (PO) performed at various ages in 25-year-old women with mutations in (A) *BRCA1* and (B) *BRCA2*, compared with women without *BRCA1/2* mutations.

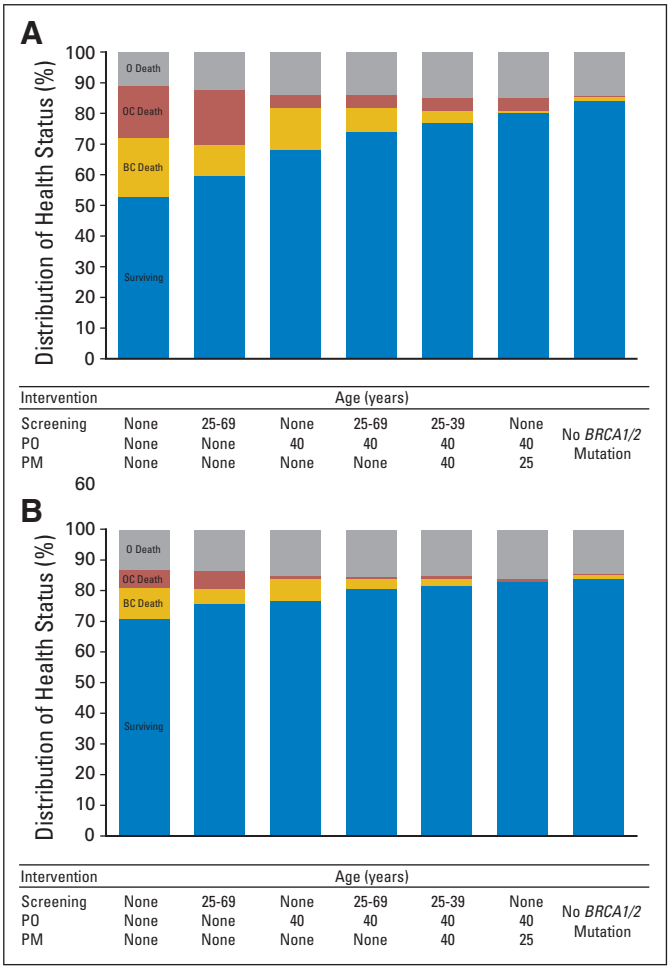

Fig 2. Distribution of health status, comprising survival probability (Surviving) and probability of death by cause, including breast cancer death (BCD), ovarian cancer death (OCD), and other-cause death (OD), by age 70 years. Interventions include screening with mammography and magnetic resonance imaging (screening), prophylactic mastectomy (PM), and prophylactic oophorectomy (PO) in 25-year-old women with mutations in (A) *BRCA1* and (B) *BRCA2*.

survival gain by 1%. Eliminating PM and substituting breast screening from ages 25 to 69 while performing PO at age 40 reduces survival gain by an incremental 2%. In the presence of PO at age 40, screening yields 3% lower survival than does PM at age 25 (80% *v* 83%), and 2% lower survival than does PM at age 40 (80% *v* 82%; Table 2). If PO is delayed to age 50, breast screening offers 4% lower survival probability than PM at age 40 (79% *v* 83%). Results by age 80 are similar (Table 2). Figure 1B presents survival probability and Figure 2B presents distribution of health status by age 70 years in *BRCA2* mutation carriers under various intervention scenarios.

Cause-Specific Mortality in BRCA2 *Mutation Carriers*

Among *BRCA2* mutation carriers who choose no intervention, more die from breast than ovarian cancer (36% *v* 20%, conditional on death by age 70), but non-cancer deaths are more frequent (44%; Table 2). With PO at age 40 only, ovarian cancer deaths decrease substantially; other-cause deaths remain most frequent (66%), followed by death from breast cancer (30%) and ovarian cancer (4%). Delaying PO from age 40 until age 50 yields little increase in ovarian cancer deaths (2% to 3%) but a larger increase in breast cancer deaths (12%). Among women who choose breast screening until age 40 and then PO plus PM at age 40, 18% will die by age 70; most (85%) die of non-cancer causes, followed by breast cancer (9%) and ovarian cancer (6%). Results are comparable for women who choose breast screening until age 69 and then PO at age 40, but not PM, and follow a similar pattern by age 80 (Table 2).

Sensitivity Analyses of Survival Probability by Age 70

We observed the largest differences in overall survival with variation in assumptions about breast cancer risk (9% to 10%), TVDT (4% to 6%), and hazard ratio for breast cancer after premenopausal oophorectomy (3% to 6%). Variation in these three parameters also yielded the greatest differences in breast cancer–specific death (13% to 22%). Ovarian cancer–specific deaths varied most with changes in breast and ovarian cancer risk and TVDT (4% to 20%). Other-cause deaths varied most with breast cancer risk, TVDT, and the hazard ratio for breast cancer after premenopausal oophorectomy in *BRCA1* mutation carriers (10% to 16%) and with breast and ovarian cancer risk and TVDT in *BRCA2* mutation carriers (9% to 15%). Variations in other model parameters yielded smaller differences in overall and cause-specific survival (Table 3).

Table 3. Sensitivity Analyses on Probability of OS, BCD, OCD, and OD by Age 70 in 25-Year-Old Women With *BRCA1/2* Mutations

Variable	OS			BCD*			OCD*			OD*		
	Base	Lower	Upper	Base	Lower	Upper	Base	Lower	Upper	Base	Lower	Upper
BRCA1												
Breast cancer risk by age 70	0.65	0.47	0.85	0.65	0.47	0.85	0.65	0.47	0.85	0.65	0.47	0.85
No screening or PM or PO	53	57	48	41	32	50	36	42	31	23	26	19
Screening, no PM or PO	59	62	57	26	19	33	46	49	41	28	32	26
Screening and PO, no PM†	74	76	70	30	22	40	15	17	13	55	61	47
Screening and PO and PM†	77	78	75	18	13	27	18	19	16	64	68	57
Ovarian cancer risk by age 70	0.39	0.39	0.46	0.39	0.39	0.46	0.39	0.39	0.46	0.39	0.39	0.46
No screening or PM or PO	53	53	50	41	41	38	36	36	41	23	23	21
Screening, no PM or PO	59	59	56	26	26	23	46	46	51	28	28	26
Screening and PO, no PM†	74	74	73	30	30	29	15	15	19	55	55	52
Screening and PO and PM†	77	77	76	18	18	18	18	18	22	64	64	60
Tumor volume doubling time, months	5.7	0.5	12	5.7	0.5	12	5.7	0.5	12	5.7	0.5	12
No screening or PM or PO	53	53	53	41	41	41	36	36	36	23	23	23
Screening, no PM or PO	59	54	60	26	38	23	46	38	47	28	24	30
Screening and PO, no PM†	74	69	74	30	42	29	15	13	16	55	45	55
Screening and PO and PM†‡	77	77	76	18	19	22	18	18	17	64	63	61
MRI sensitivity	0.85	0.50	0.90	0.85	0.50	0.90	0.85	0.50	0.90	0.85	0.50	0.90
No screening or PM or PO	53	53	53	41	41	41	36	36	36	23	23	23
Screening, no PM or PO	59	57	60	26	33	24	46	41	47	28	26	29
Screening and PO, no PM†	74	71	74	30	37	29	15	14	16	55	49	55
Screening and PO and PM†	77	76	77	18	22	17	18	17	18	64	61	65
HR for breast cancer after PO	0.5§	0.1	1	0.5§	0.1	1	0.5§	0.1	1	0.5§	0.1	1
No screening or PM or PO	53	53	52	41	40	42	36	37	36	23	23	22
Screening, no PM or PO	59	60	59	26	25	26	46	46	45	28	29	29
Screening and PO, no PM†	74	77	71	30	18	38	15	18	14	55	64	48
Screening and PO and PM†	77	77	76	18	17	20	18	18	18	64	65	62
Oral contraceptives												
HR for ovarian cancer	No use	0.5	0.5	No use	0.5	0.5	No use	0.5	0.5	No use	0.5	0.5
HR for breast cancer¶		1.0	1.5		1.0	1.5		1.0	1.5		1.0	1.5
No screening or PM or PO	53	59	55	41	49	56	36	23	20	23	28	24
Screening, no PM or PO	59	66	64	26	33	38	46	31	28	28	36	34
Screening and PO, no PM†	74	75	73	30	32	39	15	9	8	55	59	53
Screening and PO and PM†	77	79	77	18	20	26	18	10	9	64	70	65
HR for OD after PO‖	2, 1.5, 1.5	0.5, 1, 0.5	2.5, 2, 2	2, 1.5, 1.5	0.5, 1, 0.5	2.5, 2, 2	2, 1.5, 1.5	0.5, 1, 0.5	2.5, 2, 2	2, 1.5, 1.5	0.5, 1, 0.5	2.5, 2, 2
No screening or PM or PO	53	53	53	41	41	41	36	36	36	23	23	23
Screening, no PM or PO	59	60	59	26	26	26	46	46	45	28	28	29
Screening and PO, no PM†	74	75	73	30	33	29	15	16	14	55	51	55
Screening and PO and PM†	77	79	76	18	20	18	18	20	17	64	60	65
BRCA2												
Breast cancer risk by age 70	0.45	0.4	0.85	0.45	0.4	0.85	0.45	0.4	0.85	0.45	0.4	0.85
No screening or PM or PO	71	72	62	36	33	55	20	21	14	44	46	31
Screening, no PM or PO	75	76	71	21	19	37	25	25	20	54	56	43
Screening and PO, no PM†	80	81	76	18	16	35	5	5	4	77	79	61
Screening and PO and PM†	82	82	79	9	8	22	6	6	5	85	86	73
Ovarian cancer risk by age 70	0.11	0.11	0.27	0.11	0.11	0.27	0.11	0.11	0.27	0.11	0.11	0.27
No screening or PM or PO	71	71	64	36	36	28	20	20	39	44	44	33
Screening, no PM or PO	75	75	68	21	21	16	25	25	45	54	54	39
Screening and PO, no PM†	80	80	79	18	18	16	5	5	12	77	77	72
Screening and PO and PM†	82	82	80	9	9	9	6	6	13	85	85	78
Tumor volume doubling time, months	6.8	0.5	12	6.8	0.5	12	6.8	0.5	12	6.8	0.5	12
No screening or PM or PO	71	71	71	36	36	36	20	20	20	44	44	44
Screening, no PM or PO	75	72	76	21	33	20	25	21	25	54	46	55
Screening and PO, no PM†	80	78	80	18	27	17	5	4	5	77	69	78
Screening and PO and PM†‡	82	82	82	9	10	11	6	5	5	85	85	84

(continued on following page)

Table 3. Sensitivity Analyses on Probability of OS, BCD, OCD, and OD by Age 70 in 25-Year-Old Women With *BRCA1/2* Mutations (continued)

Variable	OS			BCD*			OCD*			OD*		
	Base	Lower	Upper	Base	Lower	Upper	Base	Lower	Upper	Base	Lower	Upper
MRI sensitivity	0.85	0.50	0.90	0.85	0.50	0.90	0.85	0.50	0.90	0.85	0.50	0.90
No screening or PM or PO	71	71	71	36	36	36	20	20	20	44	44	44
Screening, no PM or PO	75	74	76	21	27	20	25	23	25	54	50	55
Screening and PO, no PM†	80	79	80	18	22	17	5	5	5	77	73	78
Screening and PO and PM†	82	82	82	9	11	9	6	5	6	85	84	85
HR for breast cancer after PO	0.5§	0.1	1	0.5§	0.1	1	0.5§	0.1	1	0.5§	0.1	1
No screening or PM or PO	71	71	71	36	36	36	20	20	20	44	44	44
Screening, no PM or PO	75	75	75	21	21	21	25	25	24	54	54	55
Screening and PO, no PM†	80	82	79	18	9	25	5	6	5	77	85	70
Screening and PO and PM†	82	82	82	9	8	11	6	6	5	85	86	84
Oral contraceptives												
HR for ovarian cancer	No use	0.5	0.5	No use	0.5	0.5	No use	0.5	0.5	No use	0.5	0.5
HR for breast cancer¶		1.0	1.5		1.0	1.5		1.0	1.5		1.0	1.5
No screening or PM or PO	71	73	70	36	40	47	20	11	10	44	49	43
Screening, no PM or PO	75	78	76	21	24	30	25	14	13	54	62	57
Screening and PO, no PM†	80	81	79	18	18	24	5	3	2	77	79	74
Screening and PO and PM†	82	82	82	9	10	13	6	3	3	85	87	84
HR for OCD after PO‖	2, 1.5, 1.5	0.5, 1, 0.5	2.5, 2, 2	2, 1.5, 1.5	0.5, 1, 0.5	2.5, 2, 2	2, 1.5, 1.5	0.5, 1, 0.5	2.5, 2, 2	2, 1.5, 1.5	0.5, 1, 0.5	2.5, 2, 2
No screening or PM or PO	71	71	71	36	36	36	20	20	20	44	44	44
Screening, no PM or PO	75	75	75	21	21	21	25	25	24	54	54	55
Screening and PO, no PM†	80	82	79	18	20	17	5	6	5	77	74	78
Screening and PO and PM†	82	84	81	9	11	9	6	6	5	85	83	86

NOTE. Interventions are screening, PM, and PO at age 40. Screening consists of mammography and MRI annually, according to national practice guidelines[3,4]; it is initiated at age 25 and continued through age 69 unless PM occurs, after which time breast screening stops.

Abbreviations: OS, overall survival; BCD, breast cancer death; OCD, ovarian cancer death; OD, other-cause death; PM, prophylactic mastectomy; PO, prophylactic oophorectomy; MRI, magnetic resonance imaging; HR, hazard ratio.

*Probability of death as a result of breast cancer, ovarian cancer, or other causes, given death by age 70 or 80, expressed as a percent.

†Prophylactic surgeries (PM and/or PO) are performed at age 40 in these scenarios.

‡For women who undergo PM, this one-way sensitivity analysis on mean tumor volume doubling time yields a finding of more breast cancers at the time of PM when the mean tumor volume doubling time is larger, because in this case, more tumors are present at < 2 mm (when they are assumed to be undetectable by screening but would be found at PM) at any given time; this is a manifestation of length-time bias.

§In the base case, the HR for breast cancer is 0.50 after PO is performed between ages 40 and 50, as described in Table 1.

¶In the base case, we assumed no use of oral contraceptives (which is equivalent to an assumption of use, with no effect on breast or ovarian cancer risk). For sensitivity analysis, we assumed that women used oral contraceptive pills for at least 5 years: for the lower bound, this use was assumed to convey an HR of 0.5 for ovarian cancer with no change in the risk of breast cancer, and for the upper bound, this use was assumed to convey an HR of 0.5 for ovarian cancer with an HR of 1.5 for breast cancer.[26-36]

‖HRs for death as a result of cardiovascular disease, hip fracture, and dementia, respectively, after PO is performed at age 40.

DISCUSSION

We developed a Monte Carlo model to simulate and compare different strategies for reducing cancer mortality in *BRCA1/2* mutation carriers. The most effective strategy is PO at age 40 plus PM at age 25; for *BRCA1* mutation carriers, this approach substantially improves survival by age 70 (79% *v* 53%, with no intervention), while for *BRCA2* mutation carriers, the absolute increase is smaller (83% *v* 71%) because of their lesser cancer risks. We evaluated a delay in PO until age 50, which is 10 years later than recommended by current practice guidelines[3] but which may appeal to women because it approximates the age of natural menopause. In *BRCA1* mutation carriers, delayed PO provides half the survival gain of PO at age 40 (8% at 50 *v* 15% at 40), whereas for *BRCA2* mutation carriers, delaying PO makes less difference (4% *v* 6%). For both *BRCA1* and *BRCA2* mutation carriers, combining PO at age 40 with PM at age 25 provides survival approaching that of women without mutations (79% for *BRCA1*, 83% for *BRCA2*, and 84% for the general population); however, postponing PM until age 40, when it may prove more acceptable than at age 25, reduces survival gain by only 1% to 2%. Most notably, we found that replacing PM with MRI-based breast screening in the presence of PO at age 40 yields only a 3% to 5% decrement in survival. Approximately 36% of US *BRCA1/2* mutation carriers now choose PM, whereas 24% undergo breast screening incorporating MRI.[57] Our finding that mammography plus MRI screening offers survival probability comparable to that of PM may alter women's choices between these options. In the related field of breast cancer treatment, some women will accept adjuvant chemotherapy for an anticipated survival improvement of 5% or less, whereas others consider its side effects too morbid for such a small gain[58,59]; current research focuses on targeting chemotherapy to women with larger estimated benefits.[60]

Many prior model-based analyses have addressed cancer risk management in *BRCA1/2* mutation carriers.[19,53,61-65] Most concluded that prophylactic surgeries improve life expectancy[62,64,65]; however, few[19,63] considered recent improvements in cancer detection with breast MRI.[10-13,66] Our study represents an advance because we directly compared prophylactic surgery with screening, incorporating an updated understanding of the options available to high-risk

women. We modeled the effect of MRI screening on cancer detection and prognosis, on the basis of the tumor grade, growth rate, and hormone receptor profiles in *BRCA1*/2 mutation carriers.[10,37,38,44,67] We incorporated data on age-specific breast cancer risk reduction after premenopausal PO[6,8] and considered the use of oral contraceptives,[26-36] which most prior analyses did not. However, given controversy about chemoprevention with tamoxifen and raloxifene in *BRCA1/2* mutation carriers,[57,68-70] we did not model them. Although some practice guidelines recommend ovarian cancer screening with transvaginal ultrasound and CA125 in *BRCA1/2* mutation carriers who do not undergo PO,[3] we chose not to model this strategy, given the lack of compelling evidence that it impacts survival or other health outcomes.

As with all modeling studies, our results depend on our assumptions. We performed sensitivity analyses on all major parameters, including *BRCA1* and *BRCA2* mutation penetrance, the growth patterns of *BRCA1/2*-associated breast cancers and their detectability by screening, the impact of oral contraceptive use on breast and ovarian cancer risk, and the effect of premenopausal PO on breast cancer and other health outcomes. In sensitivity analyses, none of these factors dramatically affected the ranking of interventions but did alter our absolute estimates of overall and cause-specific survival by up to 22%. Our assumptions about breast cancer risk, breast TVDT, and the risk of breast cancer after PO at age 40 were most influential. If *BRCA1/2* mutation carriers have higher breast cancer risks than reported by large meta-analyses,[2,20] have more interval breast tumors than reported in MRI screening studies,[10-13] or gain less benefit than reported from PO at age 40,[6,49] then the survival difference between PM and MRI-based breast screening increases, although by a relatively small amount: from 3% up to 8% for *BRCA1* and from 2% to 3% for *BRCA2* mutation carriers.

Many uncertainties remain about the clinical management of *BRCA1/2* mutation carriers. Important questions include the impact of menopausal hormone therapy after premenopausal PO on breast cancer and other health outcomes, the efficacy of nipple or skin-sparing techniques compared with simple prophylactic mastectomy, the potential risk of breast cancer due to mammography, and the prognosis of *BRCA1/2*-associated cancers as targeted therapies emerge.[50,52,71-73] Answers to these questions may alter judgments about the relative efficacy and tolerability of different risk-reducing strategies and better inform future decision analyses.

Model-based analyses cannot replace empirical studies but can address clinically important questions that are poorly amenable to randomized trials. Given the complex, personal nature of decisions about prophylactic surgery, women will not likely accept random assignment between PM and breast screening; therefore, direct evidence about survival differences will remain elusive. Our analysis aims to enhance patient care by bridging the evidence gap: we provide a computer model that integrates the best available data, permitting recommendations calibrated to the variable effects of risk, age, intervention efficacy, and personal preferences. Individual women make widely disparate choices about how to manage their cancer risks, depending on their family history, health care access, reproductive concerns, and concurrent diagnoses.[18,47,57,74-76] Our results can anchor such choices quantitatively, helping a woman weigh strategies that yield small differences in survival, yet potentially larger differences in physical and emotional effects, according to her preferences. Computer-based decision support tools are now widely used to assist patients' cancer treatment choices.[58,77] Our model may similarly facilitate shared decision making, guiding women with *BRCA1/2* mutations toward better-informed choices between prophylactic surgery and screening alternatives.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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