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

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See accompanying editorial on page 189

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Submitted February 25, 2009; accepted August 25, 2009; published online ahead of print at www.jco.org on December 7, 2009.

Supported by Grants No. R01 CA829040, U01 CA088248, and R01 CA66785 from the National Institutes of Health; by Stanford University Cancer Center 2007 Developmental Research Award in Population Sciences; and by Robert Wood Johnson Foundation 2008 Physician Faculty Scholars Award (64317).

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

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0732-183X/10/2802-222/\$20.00

DOI: 10.1200/JCO.2009.22.7991

A B S T R A C T

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.

J Clin Oncol 28:222-231. © 2009 by American Society of Clinical Oncology

INTRODUCTION

More than 300,000 women in the United States are estimated to carry a mutation in the *BRCA1* or *BRCA2* genes¹; 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 prevention⁵⁻⁹ 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 carriers¹⁹ 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 MRI¹⁰⁻¹³ 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 incidence² 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 disease⁴⁰ 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 table⁵⁵ 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	Metcalf 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.

^aReported lifetime breast cancer risks were assumed to have incorporated a 30% background rate of PO at age 45 years⁷; time to second breast cancer was modeled with a Weibull distribution.

^bWe 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

^cIn 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.

^dDerived from our breast cancer natural history model using SEER data from 1975 to 1981.

^eThe 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.

^fMRI 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).

^gThe median mammography threshold applies only among women whose tumor is detectable by mammography.

^hEstimated 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*†
<i>BRCA1</i> 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
<i>BRCA2</i> 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			
Variable	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			
	OS	BCD*	OCD*	OD*†	OS	BCD*	OCD*	OD*†	OS	BCD*	OCD*	OD*†
<i>BRCA1</i> 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
<i>BRCA2</i> 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 Tables⁵⁵ 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.

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

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*.

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
<i>BRCA1</i>												
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
<i>BRCA2</i>												
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 guidelines³ 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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REFERENCES

- John EM, Miron A, Gong G, et al: Prevalence of pathogenic *BRCA1* mutation carriers in 5 US racial/ethnic groups. *JAMA* 298:2869-2876, 2007
- Antoniou A, Pharoah PD, Narod S, 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* 72:1117-1130, 2003
- National Comprehensive Cancer Network. Genetic Familial High-Risk Assessment: Breast and Ovarian. V. 1.2009. <http://www.nccn.org/>
- Saslow D, Boetes C, Burke W, et al: American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin* 57:75-89, 2007
- Domchek SM, Friebel TM, Neuhausen SL, et al: Mortality after bilateral salpingo-oophorectomy in *BRCA1* and *BRCA2* mutation carriers: A prospective cohort study. *Lancet Oncol* 7:223-229, 2006
- Eisen A, Lubinski J, Klijn J, et al: Breast cancer risk following bilateral oophorectomy in *BRCA1* and *BRCA2* mutation carriers: An international case-control study. *J Clin Oncol* 23:7491-7496, 2005
- Finch A, Beiner M, Lubinski J, et al: Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a *BRCA1* or *BRCA2* mutation. *JAMA* 296:185-192, 2006
- Kauff ND, Domchek SM, Friebel TM, et al: Risk-reducing salpingo-oophorectomy for the prevention of *BRCA1*- and *BRCA2*-associated breast and gynecologic cancer: A multicenter, prospective study. *J Clin Oncol* 26:1331-1337, 2008
- Rebeck TR, Friebel T, Lynch HT, et al: Bilateral prophylactic mastectomy reduces breast cancer risk in *BRCA1* and *BRCA2* mutation carriers: The PROSE Study Group. *J Clin Oncol* 22:1055-1062, 2004
- Kriege M, Brekelmans CT, Boetes C, et al: Efficacy of MRI and mammography for breast cancer screening in women with a familial or genetic predisposition. *N Engl J Med* 351:427-437, 2004
- Kuhl CK, Schrading S, Leutner CC, et al: Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol* 23:8469-8476, 2005
- Leach MO, Boggis CR, Dixon AK, 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* 365:1769-1778, 2005
- Warner E, Plewes DB, Hill KA, et al: Surveillance of *BRCA1* and *BRCA2* mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA* 292:1317-1325, 2004
- Bresser PJ, Seynaeve C, Van Gool AR, et al: The course of distress in women at increased risk of breast and ovarian cancer due to an (identified)

genetic susceptibility who opt for prophylactic mastectomy and/or salpingo-oophorectomy. *Eur J Cancer* 43:95-103, 2007

15. Robson M, Hensley M, Barakat R, et al: Quality of life in women at risk for ovarian cancer who have undergone risk-reducing oophorectomy. *Gynecol Oncol* 89:281-287, 2003

16. Rocca WA, Bower JH, Maraganore DM, et al: Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology* 69:1074-1083, 2007

17. Rocca WA, Grossardt BR, de Andrade M, et al: Survival patterns after oophorectomy in premenopausal women: A population-based cohort study. *Lancet Oncol* 7:821-828, 2006

18. Staton AD, Kurian AW, Cobb K, et al: Cancer risk reduction and reproductive concerns in female BRCA1/2 mutation carriers. *Fam Cancer* 7:179-186, 2008

19. Plevritis SK, Kurian AW, Sigal BM, et al: Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. *JAMA* 295:2374-2384, 2006

20. Chen S, Parmigiani G: Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol* 25:1329-1333, 2007

21. Evans DG, Shenton A, Woodward E, et al: Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: Risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. *BMC Cancer* 8:155, 2008

22. Ford D, Easton DF, Stratton M, et al: Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 62:676-689, 1998

23. King MC, Marks JH, Mandell JB: Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 302:643-646, 2003

24. Metcalfe K, Lynch HT, Ghadirian P, et al: Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol* 22:2328-2335, 2004

25. Kramer JL, Velazquez IA, Chen BE, et al: Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of BRCA1 mutation carriers. *J Clin Oncol* 23:8629-8635, 2005

26. Brohet RM, Goldgar DE, Easton DF, et al: Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: A report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. *J Clin Oncol* 25:3831-3836, 2007

27. Haile RW, Thomas DC, McGuire V, et al: BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. *Cancer Epidemiol Biomarkers Prev* 15:1863-1870, 2006

28. Jernström H, Loman N, Johannsson OT, et al: Impact of teenage oral contraceptive use in a population-based series of early-onset breast cancer cases who have undergone BRCA mutation testing. *Eur J Cancer* 41:2312-2320, 2005

29. Lee E, Ma H, McKean-Cowdin R, et al: Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: Results from a population-based study. *Cancer Epidemiol Biomarkers Prev* 17:3170-3178, 2008

30. McGuire V, Felberg A, Mills M, et al: Relation of contraceptive and reproductive history to ovarian

cancer risk in carriers and noncarriers of BRCA1 gene mutations. *Am J Epidemiol* 160:613-618, 2004

31. McLaughlin JR, Risch HA, Lubinski J, et al: Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: A case-control study. *Lancet Oncol* 8:26-34, 2007

32. Milne RL, Knight JA, John EM, et al: Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev* 14:350-356, 2005

33. Modan B, Hartge P, Hirsh-Yechezkel G, et al: Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. *N Engl J Med* 345:235-240, 2001

34. Narod SA, Dubé MP, Klijn J, et al: Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 94:1773-1779, 2002

35. Narod SA, Risch H, Moslehi R, et al: Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 339:424-428, 1998

36. Whittemore AS, Balise RR, Pharoah PD, et al: Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. *Br J Cancer* 91:1911-1915, 2004

37. Chappuis PO, Nethercot V, Foulkes WD: Clinico-pathological characteristics of BRCA1- and BRCA2-related breast cancer. *Semin Surg Oncol* 18:287-295, 2000

38. Tilanus-Linthorst MM, Obdeijn IM, Hop WC, et al: BRCA1 mutation and young age predict fast breast cancer growth in the Dutch, United Kingdom, and Canadian magnetic resonance imaging screening trials. *Clin Cancer Res* 13:7357-7362, 2007

39. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 365:1687-1717, 2005

40. Colditz GA, Willett WC, Stampfer MJ, et al: Menopause and the risk of coronary heart disease in women. *N Engl J Med* 316:1105-1110, 1987

41. Melton LJ 3rd, Khosla S, Malkasian GD, et al: Fracture risk after bilateral oophorectomy in elderly women. *J Bone Miner Res* 18:900-905, 2003

42. Berry DA, Cronin KA, Plevritis SK, et al: Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 353:1784-1792, 2005

43. Plevritis SK, Sigal BM, Salzman P, et al: A stochastic simulation model of U.S. breast cancer mortality trends from 1975 to 2000. *J Natl Cancer Inst Monogr* 36:86-95, 2006

44. Atchley DP, Albarracín CT, Lopez A, et al: Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. *J Clin Oncol* 26:4282-4288, 2008

45. National Comprehensive Cancer Network. Breast Cancer: V. 1.2009. <http://www.nccn.org/>

46. Rennett G, Bisland-Naggar S, Barnett-Griess O, et al: Clinical outcomes of breast cancer in carriers of BRCA1 and BRCA2 mutations. *N Engl J Med* 357:115-123, 2007

47. Stoller AJ, Corsetti RL: Newly diagnosed breast cancer patients choose bilateral mastectomy over breast-conserving surgery when testing positive for a BRCA1/2 mutation. *Am Surg* 71:1031-1033, 2005

48. National Comprehensive Cancer Network. Ovarian Cancer: V. 2.2009. <http://www.nccn.org/>

49. Rebbeck TR, Kauff ND, Domchek SM: Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst* 101:80-87, 2009

50. Rebbeck TR, Friebe T, Wagner T, et al: Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: The PROSE Study Group. *J Clin Oncol* 23:7804-7810, 2005

51. Rossouw JE, Anderson GL, Prentice RL, et al: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 288:321-333, 2002

52. Eisen A, Lubinski J, Gronwald J, et al: Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers. *J Natl Cancer Inst* 100:1361-1367, 2008

53. Armstrong K, Schwartz JS, Randall T, et al: Hormone replacement therapy and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: A decision analysis. *J Clin Oncol* 22:1045-1054, 2004

54. Parker WH, Broder MS, Liu Z, et al: Ovarian conservation at the time of hysterectomy for benign disease. *Obstet Gynecol* 106:219-226, 2005

55. Berkeley Mortality Database: <http://www.demog.berkeley.edu/~bmd/>

56. Centers for Disease Control, National Vital Statistics System, Worktable 292R. Death rates for 358 selected causes by 5-year age groups, race, and sex: United States, 1999-2004. http://www.cdc.gov/nchs/data/dvs/mortfinal2004_worktable292r.pdf

57. Metcalfe KA, Birenbaum-Carmeli D, Lubinski J, et al: International variation in rates of uptake of preventive options in BRCA1 and BRCA2 mutation carriers. *Int J Cancer* 122:2017-2022, 2008

58. Peele PB, Siminoff LA, Xu Y, et al: Decreased use of adjuvant breast cancer therapy in a randomized controlled trial of a decision aid with individualized risk information. *Med Decis Making* 25:301-307, 2005

59. Sweeney KJ, Ryan E, Canney M, et al: Justifying adjuvant chemotherapy in breast cancer: A survey of women and healthcare professionals. *Eur J Surg Oncol* 33:838-842, 2007

60. Goldstein LJ, Gray R, Badve S, et al: Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features. *J Clin Oncol* 26:4063-4071, 2008

61. Anderson K, Jacobson JS, Heitjan DF, et al: Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. *Ann Intern Med* 144:397-406, 2006

62. Grann VR, Jacobson JS, Thomason D, et al: Effect of prevention strategies on survival and quality-adjusted survival of women with BRCA1/2 mutations: An updated decision analysis. *J Clin Oncol* 20:2520-2529, 2002

63. Lee JM, Kopans DB, McMahon PM, et al: Breast cancer screening in BRCA1 mutation carriers: Effectiveness of MR imaging—Markov Monte Carlo decision analysis. *Radiology* 246:763-771, 2008

64. Schrag D, Kuntz KM, Garber JE, et al: Decision analysis: Effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. *N Engl J Med* 336:1465-1471, 1997

65. van Roosmalen MS, Verhoef LC, Stalmeier PF, et al: Decision analysis of prophylactic surgery or screening for BRCA1 mutation carriers: A more prominent role for oophorectomy. *J Clin Oncol* 20: 2092-2100, 2002
66. Kuhl CK, Schrading S, Bieling HB, et al: MRI for diagnosis of pure ductal carcinoma in situ: A prospective observational study. *Lancet* 370:485-492, 2007
67. Lakhani SR, Van De Vijver MJ, Jacquemier J, et al: The pathology of familial breast cancer: Predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. *J Clin Oncol* 20:2310-2318, 2002
68. Gronwald J, Tung N, Foulkes WD, et al: Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: An update. *Int J Cancer* 118: 2281-2284, 2006
69. Jones LP, Li M, Halama ED, et al: Promotion of mammary cancer development by tamoxifen in a mouse model of BRCA1-mutation-related breast cancer. *Oncogene* 24:3554-3562, 2005
70. King MC, Wieand S, Hale K, et al: Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA* 286:2251-2256, 2001
71. Sacchini V, Pinotti JA, Barros AC, et al: Nipple-sparing mastectomy for breast cancer and risk reduction: Oncologic or technical problem? *J Am Coll Surg* 203:704-714, 2006
72. Berrington de Gonzalez A, Berg CD, Visvanathan K, et al: Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers. *J Natl Cancer Inst* 101:205-209, 2009
73. Ashworth A: A synthetic lethal therapeutic approach: Poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. *J Clin Oncol* 26:3785-3790, 2008
74. Kurian AW, Hartman AR, Mills MA, et al: Opinions of women with high inherited breast cancer risk about prophylactic mastectomy: An initial evaluation from a screening trial including magnetic resonance imaging and ductal lavage. *Health Expect* 8:221-233, 2005
75. Nekhlyudov L, Bower M, Herrinton LJ, et al: Women's decision-making roles regarding contralateral prophylactic mastectomy. *J Natl Cancer Inst Monogr* 35:55-60, 2005
76. Uyei A, Peterson SK, Erlichman J, et al: Association between clinical characteristics and risk-reduction interventions in women who underwent BRCA1 and BRCA2 testing: A single-institution study. *Cancer* 107:2745-2751, 2006
77. Ravdin PM, Siminoff LA, Davis GJ, et al: Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol* 19:980-991, 2001

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