

Risk-Reducing Salpingo-Oophorectomy for the Prevention of *BRCA1*- and *BRCA2*-Associated Breast and Gynecologic Cancer: A Multicenter, Prospective Study

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A B S T R A C T

Purpose

Risk-reducing salpingo-oophorectomy (RRSO) has been widely adopted as a key component of breast and gynecologic cancer risk-reduction for women with *BRCA1* and *BRCA2* mutations. Despite 17% to 39% of all *BRCA* mutation carriers having a mutation in *BRCA2*, no prospective study to date has evaluated the efficacy of RRSO for the prevention of breast and *BRCA*-associated gynecologic (ovarian, fallopian tube or primary peritoneal) cancer when *BRCA2* mutation carriers are analyzed separately from *BRCA1* mutation carriers.

Patients and Methods

A total of 1,079 women 30 years of age and older with ovaries in situ and a deleterious *BRCA1* or *BRCA2* mutation were enrolled onto prospective follow-up studies at one of 11 centers from November 1, 1994 to December 1, 2004. Women self-selected RRSO or observation. Follow-up information through November 30, 2005, was collected by questionnaire and medical record review. The effect of RRSO on time to diagnosis of breast or *BRCA*-associated gynecologic cancer was analyzed using a Cox proportional-hazards model.

Results

During 3-year follow-up, RRSO was associated with an 85% reduction in *BRCA1*-associated gynecologic cancer risk (hazard ratio [HR] = 0.15; 95% CI, 0.04 to 0.56) and a 72% reduction in *BRCA2*-associated breast cancer risk (HR = 0.28; 95% CI, 0.08 to 0.92). While protection against *BRCA1*-associated breast cancer (HR = 0.61; 95% CI, 0.30 to 1.22) and *BRCA2*-associated gynecologic cancer (HR = 0.00; 95% CI, not estimable) was suggested, neither effect reached statistical significance.

Conclusion

The protection conferred by RRSO against breast and gynecologic cancers may differ between carriers of *BRCA1* and *BRCA2* mutations. Further studies evaluating the efficacy of risk-reduction strategies in *BRCA* mutation carriers should stratify by the specific gene mutated.

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INTRODUCTION

In 2002, two large series demonstrating efficacy of risk-reducing salpingo-oophorectomy (RRSO) for the prevention of both breast and *BRCA*-associated gynecologic (ovarian, fallopian tube and primary peritoneal) cancers were published.^{1,2} Although these and subsequent reports,³⁻⁸ have provided strong evidence that RRSO is highly protective against *BRCA*-associated cancers, almost all reports to date have examined the risk-reduction conferred by RRSO only when carriers of *BRCA1* and *BRCA2* mutations were evaluated together, or have limited

their analysis to carriers of *BRCA1* mutations alone. However, 17% to 39% of all *BRCA* mutation carriers have a mutation in *BRCA2*,^{1,2,4,7} and considerable evidence exists that carriers of *BRCA2* mutations have different risks from those of carriers of *BRCA1* mutations. Although the lifetime risk of breast cancer is similar for both *BRCA1* and *BRCA2* mutation carriers and approaches 56% to 84% by age 70,⁹⁻¹² substantial differences exist in the breast cancer phenotype seen. Only 10% to 24% of *BRCA1*-associated breast cancers are estrogen-receptor (ER) positive, whereas 65% to 79% of *BRCA2*-associated

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breast cancers are positive for this receptor.^{13,14} *BRCA1*-associated breast cancers also appear to have a characteristic gene expression profile that differs from that seen in *BRCA2*-associated breast cancers.¹⁵ Although there are fewer differences in the phenotype of *BRCA1*-associated gynecologic cancers compared with *BRCA2*-associated gynecologic cancers, the lifetime risk of gynecologic cancer differs substantially between carriers of these two genes, with 36% to 46% of *BRCA1* mutation carriers developing *BRCA*-associated gynecologic cancer by age 70 years compared with 10% to 27% of *BRCA2* mutation carriers.^{10-12,16,17}

Despite the limited data evaluating the efficacy of RRSO in women with *BRCA2* mutations alone, RRSO has been widely adopted as a cornerstone of breast and ovarian cancer risk-reduction in women with both *BRCA1* and *BRCA2* mutations.¹⁸⁻²⁰ To address the appropriateness of this uniform approach and to provide critical information for women with *BRCA2* mutations considering this procedure, we have pooled the updated data sets of two of the largest cohorts of women with *BRCA* mutations in which prospective follow-up data are available^{1,2} to provide what are, to our knowledge, the first prospective estimates of the efficacy of RRSO for the prevention of subsequent breast and *BRCA*-associated gynecologic cancers when carriers of *BRCA2* mutations are evaluated separately from carriers of *BRCA1* mutations.

PATIENTS AND METHODS

From November 1, 1994, through December 1, 2004, 1,079 women were prospectively enrolled onto ongoing follow-up studies at either Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY)^{1,21} or one of 10 academic referral centers participating in the Prevention and Observation of Surgical Endpoints (PROSE) study group.^{2,6,22} To be eligible for study inclusion, participants had to: (a) have a documented deleterious mutation in *BRCA1* or *BRCA2*; (b) have at least one ovary in situ at time of genetic testing; (c) have no personal history of *BRCA*-associated gynecologic cancer before genetic testing; and (d) be older than 30 years of age at the time of genetic testing because participation in ovarian cancer risk-reduction strategies is not generally recommended prior to this age. Participants with a personal history of breast cancer without evidence of distant metastatic disease at time of genetic testing were eligible for enrollment. Follow-up through November 30, 2005, was obtained via local center protocol and utilized a combination of mailed questionnaire, telephone contact, and medical record review. All study procedures were reviewed and approved by the relevant local institutional review boards. Additional details of the study designs for both the MSKCC^{1,21} and PROSE^{2,6,22} cohorts have been published previously.

Participants were included in the RRSO cohort if they had bilateral salpingo-oophorectomy for reasons other than known or suspected cancer after the receipt of genetic test results. The surveillance group included all women with mutations who did not elect to undergo RRSO. Although the specific method of gynecologic surveillance was not specified by protocol and there is no strategy that is known to reduce mortality from gynecologic cancers, carriers of *BRCA1* and *BRCA2* mutations have been recommended to undergo ovarian cancer screening with a combination of transvaginal ultrasound and serum CA-125 as part of usual care since 1997.²³

For women in the surveillance group, the duration of follow-up was calculated from the date of receipt of genetic test results to the date of diagnosis of new breast or *BRCA*-associated gynecologic cancer, the date of last contact, or the date of death. For women in the salpingo-oophorectomy group, the duration of follow-up was calculated from the date of salpingo-oophorectomy to the date of diagnosis of new breast or *BRCA*-associated gynecologic cancer, the date of last contact, or the date of death. If a participant initially electing surveillance was diagnosed with a new breast cancer and subsequently under-

went RRSO, they were included in the surveillance cohort for breast cancer end points and in the RRSO cohort (with follow-up beginning at time of RRSO) for gynecologic end points. Women who had a therapeutic oophorectomy because of abnormalities found during screening for ovarian cancer were included in the surveillance group, with their follow-up data censored at time of oophorectomy. For all analyses, breast cancer was defined as invasive cancer of any histologic subtype or ductal carcinoma in situ (DCIS). Gynecologic cancer was defined as invasive epithelial carcinoma of the ovary, fallopian tube, or peritoneum. Other types of breast neoplasia (eg, lobular carcinoma in situ) or gynecologic neoplasia (eg, ovarian tumors of low malignant potential, nonepithelial ovarian tumors and tumors of the uterine corpus or cervix) were not counted as events in our analysis.

Participants with bilateral breast cancer or who underwent a risk-reducing mastectomy before genetic testing were excluded from the evaluation of breast cancer end points. For participants with a history of unilateral breast cancer before genetic test results, only the contralateral breast was considered to be at risk. Participants were censored for breast cancer outcomes at time of post-results breast cancer or risk-reducing mastectomy.

To limit biases caused by inclusion of prevalent cancers, 15 participants (13 *BRCA1* mutation carriers; two *BRCA2* mutation carriers) undergoing RRSO who had an unsuspected occult gynecologic cancer diagnosed at time of risk-reducing surgery were excluded from the analysis of cancer end points. Additionally, 20 participants with breast cancer and four participants with *BRCA*-associated gynecologic cancer diagnosed within 6 months of receipt of genetic test results or RRSO were also excluded. To minimize the possibility that exclusion of these prevalent cancers would introduce a survival bias, we excluded 154 participants without a new cancer diagnosis who had less than 6 months of follow-up from receipt of genetic tests results or RRSO.

Ninety-four participants from Creighton University (Omaha, NE) and Fox Chase Cancer Center (Philadelphia, PA) were included in a recent report from the Hereditary Ovarian Cancer Clinical Study Group evaluating the impact of salpingo-oophorectomy on gynecologic cancers in women with *BRCA* mutations.⁷ Therefore, to prevent duplicate reporting, these 94 participants were excluded from the current analysis of gynecologic cancer end points and included in only the analysis of impact of RRSO on subsequent breast cancer. Lastly, because the primary goal of this study was to analyze the impact of RRSO on carriers of *BRCA1* and *BRCA2* mutations independently, four participants with mutations in both *BRCA1* and *BRCA2* were excluded.

After applying these exclusions, we identified 792 participants followed up for a mean of 39 months for gynecologic cancer events, and 597 participants followed up for a mean of 35 months for breast cancer events. Baseline demographics of the study cohorts are summarized in Tables 1 and 2.

Demographic variables were compared using *t* tests for continuous variables and the Fisher's exact test for discrete variables. A Cox proportional-hazards model²⁴ adjusted for demographic variables significantly different between the RRSO and surveillance cohorts (age at start of follow-up, parity, personal history of breast cancer, and history of prior use of hormone-replacement therapy) was used to determine the hazard ratios (HRs) for breast cancer or *BRCA*-related gynecologic cancer after RRSO. For analyses in which carriers of *BRCA1* and *BRCA2* mutations were examined together, the locus of mutation was also used as a covariate in the analysis. Statistical analyses were performed on SPSS (version 13.0; SPSS Inc, Chicago, IL) and STATA (version 8; StataCorp, College Station, TX). All reported *P* values are two sided.

RESULTS

Gynecologic Cancer

Of the 498 *BRCA1* mutation carriers and the 294 *BRCA2* mutation carriers assessable for gynecologic cancer end points, 325 *BRCA1* mutation carriers (65%) and 184 *BRCA2* (63%) mutation carriers underwent RRSO a median of 5.5 and 4.1 months, respectively, after receiving genetic test results. During 38 months of follow-up, 12 *BRCA*-associated gynecologic cancers were diagnosed a median of 37

Oophorectomy in *BRCA1* and *BRCA2* Mutation Carriers

Table 1. Demographics of Participants With Ovarian Tissue at Risk

Characteristic	RRSO Group (n = 509)		Observation/Surveillance Group (n = 283)		P
	No.	%	No.	%	
Age at start of follow-up, years					
Mean		47.1		42.9	< .001
Median		45.3		38.8	
Range		31.1-79.0		30.0-87.8	
Mutations					
<i>BRCA1</i>	325	64	173	61	.49
<i>BRCA2</i>	184	36	110	39	
Parous	419 of 507	83	203 of 280	73	.001
Prior oral contraceptive use	342 of 481	71	178 of 253	70	.86
Prior hormone replacement use	56 of 488	11	18 of 267	7	.040
Personal history of breast cancer	303	60	133	47	.001
Time to RRSO, months					
Mean		10.3		—	
Median		4.9		—	
Range		0.1-83.3		—	
Follow-up, months					
Mean		40.3		37.6	.15
Median		34.8		30.1	
Range		6.0-114.6		6.2-119.3	

Abbreviation: RRSO, risk-reducing salpingo-oophorectomy.

months after ascertainment in the 283 women undergoing surveillance. This compared with three peritoneal cancers being diagnosed a median of 16 months after RRSO during 40 months of follow-up in the 509 women electing RRSO (HR = 0.12; 95% CI, 0.03 to 0.41; $P = .001$; Table 3).

Limiting the analysis to women with *BRCA1* mutations, 10 gynecologic cancers were diagnosed in 173 *BRCA1* mutation carriers

electing surveillance. This compared with three primary peritoneal cancers developing in the 325 *BRCA1* mutation carriers electing RRSO (HR = 0.15; 95% CI, 0.04 to 0.56; $P = .005$).

In the 294 participants with *BRCA2* mutations, two *BRCA*-associated gynecologic cancers developed in the 110 women electing surveillance during 34 months follow-up. No peritoneal cancers were observed during 39 months of follow-up in the 184

Table 2. Demographics of Participants With Both Breast and Ovarian Tissue at Risk

Characteristic	RRSO Group (n = 303)		Observation/Surveillance Group (n = 294)		P
	No.	%	No.	%	
Age at start of follow-up, years					
Mean		47.7		42.8	< .001
Median		45.9		39.0	
Range		31.5-79.0		30.0-87.8	
Mutations					
<i>BRCA1</i>	190	63	178	61	.61
<i>BRCA2</i>	113	37	116	39	
Parous	244 of 301	81	217 of 291	75	.06
Prior oral contraceptive use	200 of 281	71	186 of 260	72	.99
Prior hormone replacement use	43 of 290	15	19 of 280	7	.003
Personal history of breast cancer	143	47	109	37	.013
Time to RRSO, months					
Mean		4.6		—	
Median		9.8		—	
Range		0.1-82.7		—	
Follow-up, months					
Mean		36.4		33.2	.11
Median		29.8		25.3	
Range		6.0-111.3		6.0-119.3	

Abbreviation: RRSO, risk-reducing salpingo-oophorectomy.

Table 3. Hazard Ratio for the Development of *BRCA*-Associated Gynecologic Cancer After RRSO

Mutation	No. of Patients	No. of Women Electing RRSO	Mean FU (months)	No. of Gynecologic Cancers After RRSO	No. of Women Electing Surveillance	Mean FU (months)	No. of Gynecologic Cancers During Surveillance	Hazard Ratio	95% CI	<i>P</i>
<i>BRCA1</i> and <i>BRCA2</i>	792	509	40.3	3	283	37.6	12	0.12	0.03 to 0.41	.001
<i>BRCA1</i>	498	325	41.1	3	173	40.1	10	0.15	0.04 to 0.56	.005
<i>BRCA2</i>	294	184	39.0	0	110	33.7	2	0.00	Not estimable	

Abbreviations: RRSO, risk-reducing salpingo-oophorectomy; FU, follow-up.

women with *BRCA2* mutations electing RRSO (HR = 0.00; 95% CI, not estimable).

Breast Cancer

Of 597 participants assessable for breast cancer end points, 303 underwent RRSO a median of 4.6 months after receiving genetic test results. During 33 months follow-up, 28 breast cancers (18 invasive, seven DCIS, three pathology unavailable) were diagnosed a median of 23 months after ascertainment in the 294 women electing surveillance. This compared with 19 breast cancers (16 invasive, three DCIS) being diagnosed a median of 23 months after RRSO during 36 months follow-up in the 303 women electing RRSO (HR = 0.53; 95% CI, 0.29 to 0.96; *P* = .036; Table 4).

Limiting the analysis to the 368 *BRCA1* mutations carriers in the cohort, 190 underwent RRSO a median of 5.0 months after receipt of genetic test results. Nineteen of 178 participants electing surveillance developed a new breast cancer. This compared with 15 breast cancers in 190 women electing RRSO (HR = 0.61; 95% CI, 0.30 to 1.22; *P* = .16).

When the 229 *BRCA2* mutation carriers were examined, 113 underwent RRSO a median of 4.0 months from receipt of genetic test results. Nine breast cancers developed in the 116 women electing surveillance versus four breast cancers in the 113 women electing RRSO. (HR = 0.28; 95% CI, 0.08 to 0.92; *P* = .036).

Pathology reports were available on 44 (94%) of 47 breast cancers diagnosed during follow-up. To examine possible reasons for the apparent difference in the magnitude of breast cancer risk-reduction between carriers of *BRCA1* mutations and carriers of *BRCA2* mutations, several exploratory analyses were conducted. When invasive and noninvasive breast cancers were examined independently, RRSO appeared to be more protective against noninvasive breast cancer (HR = 0.32; 95% CI, 0.08 to 1.25; *P* = .10) than invasive breast cancer (HR = 0.73; 95% CI, 0.37 to 1.45; *P* = .37) When the 34 known invasive cancers were examined, RRSO appeared to be protective

against ER-positive invasive breast cancer (HR = 0.22; 95% CI, 0.05 to 1.05; *P* = .058), but not ER-negative invasive breast cancer (HR = 1.10; 95% CI, 0.48 to 2.51; *P* = .82; Table 5).

DISCUSSION

The current report represents, to our knowledge, the first prospective study to evaluate the impact of RRSO on *BRCA*-associated breast and gynecologic cancer risk when carriers of *BRCA2* mutations are evaluated separately from carriers of *BRCA1* mutations. In this series, RRSO was associated with significant protection against *BRCA1*-associated gynecologic cancer and *BRCA2*-associated breast cancer. Although protection against *BRCA1*-associated breast cancers and *BRCA2*-associated gynecologic cancers was suggested, neither of these effects reached statistical significance.

In the only two retrospective studies reporting the impact of RRSO on breast cancer risk in *BRCA2* mutation carriers separately from *BRCA1* mutation carriers, RRSO was not associated with a significant reduction in total *BRCA2*-associated breast cancer risk (odds ratio [OR] = 0.57; 95% CI, 0.28 to 1.15; *P* = .11)⁴ or contralateral *BRCA2*-associated cancer risk (HR = 0.75; 95% CI, 0.16 to 3.48, *P* = .72).²⁵ A likely reason for the difference in our results and these studies is the potential for survival bias being introduced by their ascertainment strategies.²⁶ In other studies that have evaluated the impact of ovarian hormone modification, via tamoxifen, on *BRCA2*-associated breast cancer risk, there has been a consistent suggestion of benefit of tamoxifen use in *BRCA2* mutation carriers.^{27,28}

Although the current study did not conclude that RRSO was associated with a statistically significant risk-reduction against *BRCA1*-associated breast cancer, an effect comparable to what has been seen in prior studies evaluating *BRCA1* mutation carriers alone was suggested.^{4,5,29} Given this consistent effect across studies and the preponderance of ER-negative breast cancer seen in *BRCA1* mutation

Table 4. Hazard Ratio for the Development of *BRCA*-Associated Breast Cancer After RRSO

Mutation	No. of Patients	No. of Women Electing RRSO	Mean FU (months)	No. of Breast Cancers After RRSO	No. of Women Electing Surveillance	Mean FU (months)	No. of Breast Cancers During Surveillance	Hazard Ratio	95% CI	<i>P</i>
<i>BRCA1</i> and <i>BRCA2</i>	597	303	36.4	19	294	33.2	28	0.53	0.29 to 0.96	.036
<i>BRCA1</i>	368	190	36.3	15	178	34.0	19	0.61	0.30 to 1.22	.16
<i>BRCA2</i>	229	113	36.6	4	116	31.9	9	0.28	0.08 to 0.92	.036

Abbreviations: RRSO, risk-reducing salpingo-oophorectomy; FU, follow-up.

Table 5. Hazard Ratio for the Development of Invasive ER-Positive and ER-Negative Breast Cancer After RRSO

Technique	No. of Patients	ER-Positive Invasive Breast Cancer				ER-Negative Invasive Breast Cancer			
		Events	Hazard Ratio	95% CI	<i>P</i>	Events	Hazard Ratio	95% CI	<i>P</i>
RRSO	300	2	0.22	0.05 to 1.05	.058	14	1.10	0.48 to 2.51	.85
Surveillance	284	7	1.0	Referent		11	1.0	Referent	

Abbreviations: ER, estrogen receptor; RRSO, risk-reducing salpingo-oophorectomy.

carriers, several authors have hypothesized that ovarian hormone ablation might influence the tumorigenesis of *BRCA*-associated, ER-negative breast cancer.^{4,28,30,31} In the current report, however, RRSO appeared to be protective against ER-positive but not ER-negative disease, calling this hypothesis into question. Although this analysis was limited by the small number of events in each group, these results are consistent with other studies evaluating selective ER modulators and aromatase inhibitors for the prevention of subsequent breast cancer in women without known *BRCA* mutations.³²⁻³⁴

Our results confirm that RRSO is associated with substantial protection against *BRCA1*-associated gynecologic cancer. The relatively low incidence of *BRCA2*-associated gynecologic cancers in the cohort (two in the surveillance cohort, zero in the RRSO cohort) limits conclusions regarding the impact of RRSO on the risk of subsequent *BRCA2*-associated gynecologic cancers. The low absolute number of *BRCA2*-associated gynecologic cancers, however, may have important implications for women comparing the relative risks and benefits of specific gynecologic cancer risk-reduction strategies.

The current report has a number of limitations. Although the ideal study design to evaluate the efficacy of RRSO for the prevention of subsequent breast and gynecologic cancer would be a prospective randomized trial, such a trial would almost certainly not be feasible for a risk-reducing surgical intervention. As reviewed by Klaren,²⁶ the prospective cohort design used here has the least potential for substantial bias, but is still subject to potential detection or lead-time bias. To minimize the possibility of a detection bias, participants with cancer diagnosed within the first 6 months after genetic testing or RRSO were excluded from the analysis. If these participants and all women with less than 6 months of follow-up are included in the analysis, the inferences were not changed for any of our analyses. RRSO remained protective against *BRCA1*-associated gynecologic cancer (HR = 0.11; 95% CI, 0.03 to 0.39; *P* = .001) and *BRCA2*-associated breast cancer (HR = 0.27; 95% CI, 0.09 to 0.75; *P* = .013). Although a protection against *BRCA1*-associated breast cancer was again suggested, this result still did not achieve statistical significance (HR = 0.68; 95% CI, 0.38 to 1.22; *P* = .19). Similarly, to prevent duplicate publication, 94 participants from Creighton University and Fox Chase Cancer Center included in a recent report from Finch et al⁷ were excluded from the analysis of gynecologic cancer end points. If these participants are included, the protection conferred by RRSO against *BRCA*-associated gynecologic cancer in *BRCA1* and *BRCA2* mutation carriers combined (HR = 0.11; 95% CI, 0.03 to 0.37; *P* < .001) and *BRCA1* mutation carriers alone (HR = 0.13; 95% CI, 0.04 to 0.46; *P* = .002) remains essentially unchanged.

Although a personal history of breast cancer at time of accrual was treated as a covariate in the Cox proportional-hazards model, it is possible that inclusion of participants with

a prior history of breast cancer still introduced a potential bias into the analyses. Limiting the analyses to participants without a personal history of breast cancer at time of accrual, RRSO appeared to confer a similar magnitude of protection against a first breast cancer in both the 220 *BRCA1* mutation carriers without prior breast cancer (HR = 0.49; 95% CI, 0.15 to 1.53; *P* = .22) and the 125 *BRCA2* mutation carriers without prior breast cancer (HR = 0.27; 95% CI, 0.05 to 1.48; *P* = .13), as was seen in the entire cohort. It is also possible that the biologic effects of other demographic variables significantly different between the RRSO and surveillance groups (ie, age at study entry, parity, and history of prior hormone replacement) might not have been entirely corrected for by treating these as covariates in the analyses. Further exploration of this issue awaits the result of prospective studies large enough to match participants for these potentially important differences.

The exploratory analysis examining the impact of RRSO on subsequent ER-positive and ER-negative breast cancer is limited by small numbers, lack of central pathology review, and missing histology and ER status on three of the breast cancers diagnosed during follow-up. Additionally, given the relatively short follow-up, it is possible that a component of the decrease in ER-positive breast cancer risk was caused by treatment of preexisting tumors in this subgroup, whereas prevention of ER-negative breast cancer requires ovarian hormone ablation earlier in the process of tumorigenesis. Given these limitations, the apparent differential impact of RRSO on ER-positive versus ER-negative disease should be viewed as hypothesis generating and awaits confirmation in further prospective studies.

The present report provides strong confirmation that RRSO remains the most effective risk-reduction strategy for the prevention of *BRCA1*-associated gynecologic cancer. Although protection against *BRCA2*-associated gynecologic cancer was only suggested, it is possible, given that 76% of *BRCA2*-associated ovarian cancers are diagnosed at age older than 60,³⁵ that our cohort of *BRCA2* mutation carriers, with a median age of 46 years, was not yet old enough to demonstrate a significant protection against *BRCA2*-associated gynecologic cancer. Even given this limitation, until more effective ovarian cancer surveillance is available, RRSO should be discussed with all carriers of *BRCA* mutations who have completed childbearing and have entered the risk period for gynecologic cancers. Although RRSO will likely remain an important method for reducing the risk of ER-positive breast cancer in women with mutations in *BRCA1* or *BRCA2*, its role in concert with other ovarian hormone manipulations such as tamoxifen, raloxifene, and the aromatase inhibitors remains to be elucidated. Prevention of ER-negative breast cancer remains a challenge. The optimal

strategy for reducing the risk of this important cancer in carriers of both *BRCA1* and *BRCA2* mutations will emerge from future prospective studies stratified according to genetic linkage to one or the other of these related, but distinct, cancer susceptibility syndromes.

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